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2015 guidelines for the management of hypertension. Recommendations of the Polish Society of Hypertension — short version

Zasady postępowania w nadciśnieniu tętniczym — 2015 rok. Wytyczne Polskiego Towarzystwa Nadciśnienia Tętniczego — wersja skrócona

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INTRODUCTION

The Polish Society of Hypertension (PTNT) presents a new edition of its guidelines for the management of hypertension.

During 4 years that have passed since publication of the previous 2011 guidelines, results of multiple studies and metaanalyses evaluating antihypertensive therapy have been published. These results have extended the range of available information, leading to modification of some previous concepts, such as the approach to the treatment of resistant and secondary hypertension, including interventional treatment.

The present document is generally based on the 2011 PTNT guidelines and includes some of the changes, which were considered appropriate by the authors of the present guidelines, that were introduced in the most recent European Society of Hypertension/European Society of Cardiology (ESH/ESC) guidelines published in 2013.

A novel aspect of the 2015 PTNT guidelines has been the addition of an extensive chapter on the management of hypertension in children, based on the fact that hypertension specialists in training may stem from both internists and paediatricians (available in full version), and an attempt to make this guideline edition more practical, taking into consideration some specific Polish conditions and issues regarding the diagnosis and drug treatment.

A traffic light (in original version) signalling system-based classification has been introduced in the tables summarising the basic principles of the management of hypertension in special patient populations, with the three colours corresponding in a simplified way to typical recommendation classes along with their levels of evidence, but also reflecting expert opinion to a greater degree compared to the 2013 ESH/ESC guidelines. These colours mean:

- light grey (green in original version) — a given management approach is recommended, generally based on clear evidence from research studies, or unequivocal expert opinion resulting from everyday clinical practice;
- grey (yellow in original version) — a given management approach is suggested as appropriate despite lacking or equivocal evidence from research studies, based on the opinion of the majority of experts reflecting common sense and their personal clinical experience;
- blue (red in original version) — a given management approach is considered harmful, generally based on clear evidence from research studies, or not justified due to lack of supporting evidence.

1. EPIDEMIOLOGY AND PREVENTION OF HYPERTENSION

Hypertension remains the most important risk factor for premature mortality worldwide. Blood pressure (BP) values show a linear correlation with mortality and the incidence of cardiovascular disease (CVD — myocardial infarction [MI], stroke, heart failure [HF], peripheral vascular disease) and chronic kidney disease (CKD) in all age and ethnic groups in both women and men.

Data obtained during the last 20 years indicate an increasing prevalence of hypertension in Poland. The NATPOL 2011 study showed that over 10 years, the prevalence of hypertension in individuals aged 18–79 years increased from 30% to 32%, or approximately 9 million. In addition, the POLSENIOR study indicates that hypertension is present in about one million of people above 80 years of age. If these trends continue, it has been estimated that the number of subjects with hypertension will have increased by half until 2035.

Development of hypertension may be best prevented by interventions targeted at environmental factors. The most effective approach to prevent or delay development of hypertension (primary prevention) is lifestyle modification, in particular prevention of obesity and increasing physical activity. Primary prevention may be divided into population efforts, directed at the general population, and prevention targeted at those at an increased risk of hypertension. The latter should focus on the following groups:

- subjects with a family history of premature CVD (stroke, MI, HF) — below 65 years of age in women and 55 years of age in men;
- patients with diabetes or concomitant kidney disease;
- subjects with two or more conventional cardiovascular (CV) risk factors;
- subjects with high normal BP (≥ 130/85 mm Hg);
- subjects with white coat hypertension.

About 30% of subjects are unaware of hypertension which results from the fact that nearly 40% of people in Poland do not know their BP values. Due to this low identification of hypertension in Poland, screening BP measurements are recommended in all adults at least once a year regardless of previous BP values. The proportion of subjects with the diagnosis of hypertension who remained untreated decreased from 18% to 13%. A positive trend has been also the observed increase in the proportion of hypertensive subjects with adequately controlled BP from 12% to 26%. This is related to the fact that the proportion of adequate BP control among treated subjects increased from 22% to 42%.

2. DIAGNOSIS AND CLASSIFICATION

Hypertension may be diagnosed if average BP values (calculated based on at least two measurements on **at least two** different visits) are equal to or higher than **140 mm Hg** (SBP, systolic blood pressure) and/or **90 mm Hg** (DBP, diastolic blood pressure).

In patients with BP values below 160/100 mm Hg, the diagnosis of hypertension should be confirmed by ambulatory blood pressure monitoring (ABPM) or, if this method is not available, by home BP measurements, using different threshold values as shown in Table 1.

Table 1. Diagnosis of hypertension based on office and out-of-office blood pressure (BP) measurements

Category	Systolic BP [mm Hg]		Diastolic BP [mm Hg]
Office BP measurements	≥ 140	and/or	≥ 90
Ambulatory BP measurements			
— daytime (or awake)	≥ 135	and/or	≥ 85
— nighttime (or sleep)	≥ 120	and/or	≥ 70
— mean 24-h	≥ 130	and/or	≥ 80
Home BP measurements	≥ 135	and/or	≥ 85

Table 2. Definitions and classification of office blood pressure (BP) levels

Category	Systolic BP [mm Hg]		Diastolic BP [mm Hg]
Optimal BP	< 120	and	< 80
Normal BP	120–129	and/or	80–84
High normal BP	130–139	and/or	85–89
Grade 1 hypertension	140–149	and/or	90–99
Grade 2 hypertension	160–179	and/or	100–109
Grade 3 hypertension	≥ 180	and/or	≥ 110
Isolated systolic hypertension	≥ 140	and	< 90

In patients with BP values ≥ 180/≥ 110 mm Hg, the diagnosis of hypertension may be made at the first visit after excluding the effect of factors leading to acute BP elevation, e.g. anxiety, pain, or alcohol intake.

The diagnosis of hypertension may also be made based on reliable data from the history or patient medical records (BP values or the use of antihypertensive medications).

In the present 2015 PTNT guidelines, we retained the previous classification of hypertension based on office BP measurements, with three grades of severity and the separate subtype of isolated systolic hypertension (ISH). The classification also continues to categorise BP values in the normal range into optimal, normal, and high normal BP.

Detailed classification of hypertension is shown in Table 2.

Blood pressure values are of major importance when stratifying patient risk. The remaining components required for this assessment must be obtained by the physician based on history, physical examination, and laboratory tests.

3. INVESTIGATIONS

At the time of the diagnosis of hypertension, all patients should undergo comprehensive evaluation that includes detailed history, physical examination, and selected laboratory tests and other investigations as required.

The goals of clinical evaluation include identification of:

— other concomitant CV risk factors;
— target organ damage and the presence and severity of other diseases, including CVD, kidney disease, and diabetes;
— the cause of elevated BP and indications for investigating for possible secondary hypertension.

3.1. Laboratory investigations

Laboratory investigations include **routine** tests necessary in all patients with hypertension, **additional** tests performed in selected patients, and **specialist** tests performed during more extensive diagnostic work-up in reference centres are shown in Table 3.

3.2. Ambulatory blood pressure monitoring

Increasing the number of BP measurements performed out-of-office, in conditions that reflect the usual patient environment, allows more reliable evaluation of actual BP values. Different diagnostic thresholds for out-of-office measurements compared to office measurements have been included in the diagnostic criteria for hypertension. Normal BP by ABPM is defined as mean daytime values below 135/85 mm Hg, mean nighttime values below 120/70 mm Hg, and mean 24-h values below 130/80 mm Hg. Mean BP values obtained by ABPM or home blood pressure monitoring (HBPM) better reflect the risk of CV events and correlate more strongly with the presence of subclinical target organ damage compared to office BP values. Out-of-office measurements allow the diagnosis of masked hypertension, which is characterised by elevated BP values only in ABPM or HBPM, and are necessary for modifications of the timing of antihypertensive drug administration. Despite clear clinical utility, ABPM also has some limitations including high cost, still suboptimal availability, and unclear reproducibility of findings (though the latter is higher compared to office BP measurements). To obtain reliable measurements, validated devices should be used, and care should be taken to ensure proper measurement technique.

Table 3. Routine, additional, and specialist laboratory investigations in hypertensive patients (according to ESH/ESC)

Routine tests
Full blood count
Fasting plasma glucose
Serum total cholesterol, LDL-C, HDL-C, and triglycerides
Serum potassium, sodium, and uric acid
Serum creatinine (with estimation of GFR)
Urine analysis; albuminuria
12-lead electrocardiogram
Additional tests
Echocardiography
Carotid and renal artery ultrasound
Quantitative evaluation of proteinuria (if positive reagent strip test); urinary sodium and potassium
Fundoscopy
Oral glucose tolerance test
24-h ambulatory blood pressure monitoring
24-h Holter monitoring if arrhythmias
Ankle-brachial index measurement
Pulse wave velocity measurement
Specialist tests
Further search for cerebral, cardiac, renal and vascular damage, mandatory in resistant or complicated hypertension
Search for secondary hypertension when suggested by clinical evidence or results of previous investigations

GFR — glomerular filtration rate; HDL-C — high-density lipoprotein cholesterol; LDL-C — low-density lipoprotein cholesterol

The use of ABPM has increased in the recent years, as reflected by extended indications for this investigation in the 2011 British Society of Hypertension (BSH)/National Institute for Clinical Excellence (NICE) guidelines and the 2013 ESH/ESC guidelines. ABPM allow detection of prognostically adverse phenomena including excessive morning BP surge, and non-dipper and extreme-dipper patterns of the circadian BP rhythm. Clearly, ABPM should be widely used to diagnose hypertension, particularly in patients with grade 1 hypertension by office BP measurements. Specific indications for ABPM are listed in Table 4.

3.3. Home blood pressure measurements

Home BP measurements not only reduce the risk of a white-coat effect, often observed during office BP measurements, but also show good agreement with daytime ABPM measurements. In addition, home BP values correlate with CV risk better than office values. **Abnormal home BP values are defined as the average of several measurements greater than or equal to 135 mm Hg and/or 85 mm Hg.**

Table 4. Indications for and technique of ambulatory blood pressure measurements (ABPM)

Indications for ABPM
Confirmation of the diagnosis of hypertension in patients with grade 1 hypertension by office BP measurements and low/moderate cardiovascular risk
Suspicion of white-coat hypertension
— grade 1 hypertension by office BP measurements
— long-standing hypertension without target organ damage and/or with low global cardiovascular risk
— large BP differences in office measurements (> 20 mm Hg) or differences between home and office readings
Suspicion of masked hypertension
— high normal BP by office measurements
— normal office BP readings in individuals with subclinical target organ damage or high global cardiovascular risk
— suspicion of nocturnal hypertension and/or abnormal 24-h BP pattern
Suspicion of hypotension (dizziness, falls, presyncope, syncope) or autonomic system dysfunction
Identification of true resistant or pseudo resistant hypertension
— suspicion of white-coat effect in treated hypertensives
Hypertension in pregnant women
Hypertension in patients with glaucoma
Technique of ABPM
First, measure BP on both arms with a conventional sphygmomanometer according to the general principles
Depending on BP difference between arms:
≤ 10 mm Hg (SBP) — place the cuff on the non-dominant arm
> 10 mm Hg — place the cuff on the arm with higher BP reading
Choose an appropriately-sized cuff and measure BP using the automated device
If the difference between initial BP reading and BP read by the automated device is greater than 5 mm Hg, re-adjust the cuff
Set BP measurement intervals (preferred intervals 15–20 min during the day and 30 min during the night, maximum acceptable intervals 30 min during the day and 60 min during the night)
Switch off BP reading display
Provide the patient with a diary to record activity during the monitoring (along with a contact phone number)
A recording is acceptable if it includes at least 70% of the planned BP readings during the day and night

BP — blood pressure; SBP — systolic blood pressure

During long-term management, 1–2 measurements per week are recommended, with values recorded in a patient diary. Daily home measurements should be advised during the week prior to a follow-up visit (2 measurements in the morning and 2 measurements in the evening, before

Table 5. Risk factors, target organ damage, and metabolic, cardiovascular, and renal disease used for stratification of the global cardiovascular risk (see Fig. 1)

Risk factors
Male sex
Age (men ≥ 55 years, women ≥ 65 years)
Smoking
Dyslipidaemia:
— total cholesterol > 4.9 mmol/L (190 mg/dL), and/or
— LDL cholesterol > 3.0 mmol/L (115 mg/dL), and/or
— HDL cholesterol < 1.0 mmol/L (40 mg/dL) in men, < 1.2 mmol/L (46 mg/dL) in women, and/or
— triglycerides > 1.7 mmol/L (150 mg/dL)
Fasting plasma glucose 5.6–6.9 mmol/L (102–125 mg/dL)
Abnormal glucose tolerance test
Obesity (BMI ≥ 30 kg/m^2)
Abdominal obesity (waist circumference: men ≥ 102 cm, women ≥ 88 cm — in Caucasians)
Family history of premature CVD (men < 55 years, women > 65 years)
Subclinical target organ damage
Pulse pressure (in the elderly) ≥ 60 mm Hg
Electrocardiographic LVH
— Sokolov–Lyon index > 3.5 mV
— R in aVL > 1.1 mV
— Cornell voltage duration product > 244 mV × ms
or echocardiographic LVH
— LVM index > 115 g/m^2 BSA in men, > 95 g/m^2 BSA in women
Carotid artery wall thickening (IMT > 0.9 mm) or the presence of a atherosclerotic plaque
Carotid artery-femoral artery PWV > 10 m/s
Ankle–brachial index < 0.9
Chronic kidney disease with eGFR 30–60 mL/min/1.73 m^2 BSA
Albuminuria 30–300 mg/24 h or urinary albumin-creatinine ratio 30–300 mg/g (3.4–34 mg/mmol) (preferentially on morning spot urine)
Diabetes
Fasting plasma glucose ≥ 7.0 mmol/L (126 mg/dL) on two measurements
Random glucose ≥ 11.1 mmol/L (200 mg/dL) if symptoms of hyperglycaemia are present, such as polydipsia, polyuria, fatigue
Post-load plasma glucose ≥ 11.1 mmol/L (200 mg/dL)
Overt cardiovascular or renal disease
Cerebrovascular disease: ischaemic stroke, cerebral haemorrhage, TIA
CVD: myocardial infarction, angina, myocardial revascularisation with PCI or CABG
Heart failure, including heart failure with preserved EF
Symptomatic lower extremities peripheral arterial disease
Chronic kidney disease with eGFR < 30 mL/min/1.73 m^2 BSA, proteinuria > 300 mg/24 h
Advanced retinopathy: haemorrhages or exudates, papilledema

BMI — body mass index; BSA — body surface area; CABG — coronary artery bypass grafting; CVD — cardiovascular disease; EF — ejection fraction; eGFR — estimated glomerular filtration rate; HDL — high-density lipoprotein; IMT — intima–media thickness; LDL — low-density lipoprotein LVH — left ventricular hypertrophy; LVM — left ventricular mass; PCI — percutaneous coronary intervention; PWV — pulse wave velocity; TIA — transient ischaemic attack

Clinical profile	Blood pressure [mm Hg]			
	High normal (130–139/85–89)	Grade 1 hypertension (140–159/90–99)	Grade 2 hypertension (160–179/100–109)	Grade 3 hypertension (≥ 180/110)
No risk factors	Average*	Low	Moderate	High
1–2 risk factors	Low	Moderate	Moderate	High
≥ 3 risk factors	Moderate	Moderate	High	High
Target organ damage, diabetes, CKD stage 3	High	High	High	Very high
Overt cardiovascular disease, CKD stage ≥ 4	Very high	Very high	Very high	Very high

Figure 1. Evaluation of the global cardiovascular (CV) risk in hypertensive patients
*Denotes CV risk in the healthy population, which is lower than a "low" global cardiovascular risk in respective age groups
CKD — chronic kidney disease (stage 3: eGFR 30–59 mL/min/1.73 m^2; stage ≥ 4: eGFR < 30 mL/min/1.73 m^2)

medication intake) and are a basis for medication adjustments by a physician.

3.4. Assessment of the global cardiovascular risk

In most patients, other concomitant factors affecting the global CV risk may be detected at the time of the diagnosis of hypertension. Thus, the management of a hypertensive patient should include estimation of CV risk based on the severity of hypertension and the presence of other major risk factors, subclinical target organ damage, and concomitant diabetes, CVD, or CKD. The risk is then categorised as low, moderate, high, or very high. **Assessment of the global CV risk is the basis of therapeutic choices regarding many aspects of the management and treatment strategy in a hypertensive patient.**

Table 5 summarises risk factors, subclinical target organ damage, CVD and kidney disease taken into account when evaluating the risk of a CV event, and stratification of the global risk based on these factors is shown in Figure 1.

When based on the Framingham model, interpretation of the level of risk (low, moderate, high, or very high), which is higher compared to healthy subjects without risk factors, indicates that the 10-year absolute risk of CVD is below 15%, 15–20%, 20–30%, and above 30%, respectively. Using the European Systematic Coronary Risk Evaluation (SCORE) model, the 10-year absolute risk of CV death for the above risk categories is below 4%, 4%, 5–8%, and above 8%, respectively. Use of the SCORE risk chart is recommended in subjects above 40 years of age free from CVD and diabetes. For younger subjects, a relative risk chart is available (see: Eur Heart J, 2012; 33: 1635–1701).

In patients with an abnormal circadian BP pattern (non-dippers, extreme dippers), the global risk is increased in relation to the observed BP values.

In patients with masked hypertension, the global risk is similar to that in subjects with office hypertension. In contrast, the risk in those with white-coat hypertension is lower than indicated by office BP measurements.

4. THERAPEUTIC MANAGEMENT

4.1. Overall goals and principles of the management

The basic goal of treatment in patients with hypertension is to reduce mortality and the global risk of CV and renal complications. In particular, drug treatment should reduce BP values to target levels established for hypertensives or, if it is not feasible, as close to these values as possible. This is based on numerous observations that effective BP lowering reduces the risk of CV events, particularly stroke and acute coronary events, and delays progression of renal disease. **At the same time, global treatment strategy in the hypertensive patient should include correcting all other modifiable CV risk factors.**

4.1.1. Initiation of antihypertensive therapy

The decision to initiate antihypertensive therapy should be preceded by history taking and physical examination, including BP measurements according to the above defined standards. If grade 3 (BP ≥ 180 and/or 110 mm Hg) or grade 2 (BP ≥ 160 and/or 100 mm Hg) hypertension is found, as confirmed by at least two measurements at one or two occasions, respectively, drug treatment should be initiated immediately along with necessary non-pharmacological measures, prior to complete evaluation of the risk profile.

If the observed BP values indicate grade 1 hypertension (140–159/90–99 mm Hg), non-pharmacological measures should be instituted, and the decision to initiate drug therapy should be made after comprehensive risk stratification and evaluation of the effects of non-drug treatment, and if the global CV risk is low or moderate, also following additional verification of the diagnosis of hypertension by ABPM. This indicates that it is not necessary to start drug treatment in patients with white-coat hypertension, and only lifestyle changes and periodic reevaluation by ABPM should be recommended instead, as these individuals are at an increased risk of developing true hypertension. Despite little evidence of benefits of antihypertensive therapy in patients with grade 1 hypertension, there are arguments in favour of initiating drug treatment at some point also in these patients, as summarised in the 2013 ESH/ESC guidelines: (i) withholding drug therapy leads over time to an increase in the global risk which is difficult to reverse, (ii) appropriately individualised antihypertensive drug therapy is effective and well tolerated long-term, and (iii) cheap antihypertensive drugs are available that provide a good benefit-to-cost ratio.

If grade 1 hypertension is confirmed in an elderly patient, the decision to initiate drug treatment should be more cautious and is not obligatory due to the fact that evidence of benefits of antihypertensive drug therapy in this age group come from studies that recruited patients with at least grade 2 hypertension. On the other hand, elderly patients constituted a significant proportion of patient populations in many large-scale clinical trials that showed benefits of antihypertensive drug therapy.

The 2013 ESH/ESC guidelines suggested that lifestyle changes only should be instituted in young subjects with grade 1 ISH, as there is no evidence of treatment benefits in this age group, and their central aortic pressure is often normal. It seems that the decision to initiate drug treatment in these patients should be individualised based on the evaluation of their global CV risk, possibly measurement of central BP, and after mandatory verification of the diagnosis of hypertension by ABPM.

Routine antihypertensive drug therapy in patients with high normal BP (130–139/85–89 mm Hg) continues to be considered unnecessary regardless of the presence of metabolic syndrome, diabetes, and/or CVD (ischaemic heart disease [IHD], previous MI or stroke). In the latter group, antihyper-

<table>
<tr><th rowspan="2">Clinical profile</th><th colspan="4">Blood pressure [mm Hg]</th></tr>
<tr><th>High normal
(130–139/85–89)</th><th>Grade 1 hypertension
(140–159/90–99)</th><th>Grade 2 hypertension
(160–179/100–109)</th><th>Grade 3 hypertension
(≥ 180/110)</th></tr>
<tr><td></td><td colspan="4">Non-drug therapy and antihypertensive drug therapy</td></tr>
<tr><td>No risk factors</td><td>No intervention</td><td rowspan="2">Lifestyle changes: confirmation by ABPM if BP ≥ 140/90 after 3 months, then add drugs</td><td rowspan="2">Lifestyle changes + drug treatment starting from the 2nd visit</td><td rowspan="5">Lifestyle changes + drug treatment starting from the 1st visit</td></tr>
<tr><td>1–2 risk factors</td><td>Lifestyle changes</td></tr>
<tr><td>≥ 3 risk factors</td><td>Lifestyle changes</td><td>Lifestyle changes: confirmation by ABPM if BP ≥ 140/90 after 3 months, then add drugs</td><td>Lifestyle changes + drug treatment starting from the 2nd visit</td></tr>
<tr><td>Target organ damage, diabetes, CKD stage 3</td><td>Lifestyle changes*</td><td>Lifestyle changes + drug treatment starting from the 1st visit</td><td>Lifestyle changes + drug treatment starting from the 1st visit</td></tr>
<tr><td>Overt cardiovascular disease, CKD stage ≥ 4</td><td>Lifestyle changes*</td><td>Lifestyle changes + drug treatment starting from the 1st visit</td><td>Lifestyle changes + drug treatment starting from the 1st visit</td></tr>
</table>

Figure 2. Initiation of antihypertensive therapy in relation to blood pressure (BP) values and the global cardiovascular risk
*In the high normal BP range, antihypertensive drugs are often indicated for reasons other than elevated BP (treatment of cardiac events, cardiovascular prevention, nephroprotection)
ABPM — ambulatory blood pressure measurements; CKD — chronic kidney disease (stage 3: eGFR 30–59 mL/min/1.73 m^2; stage ≥ 4: eGFR < 30 mL/min/1.73 m^2)

tensive drug may be necessary for other indications (secondary prevention of MI, treatment of HF, nephroprotection).

Non-drug treatment involving lifestyle changes is a necessary component of the management of hypertension and should be initiated at the first visit in all patients with suspected hypertension, including those with high normal BP. Initiating drug treatment does not mean that lifestyle changes are no longer necessary. At the same time, due to low patient compliance regarding lifestyle changes, institution of non-drug treatment should not delay the decision to initiate antihypertensive drug therapy beyond the time limits set for this decision, particularly in patients with higher CV risk.

The principles of initiating drug therapy are summarised in Figure 2.

4.1.2. Target blood pressure

Target BP is a threshold value below which patient's BP should be kept during optimal antihypertensive therapy. Only once target BP values are reached, there is no need for further therapy intensification. In the past, recommendations regarding target BP values were often changed with publication of the results of large trials comparing benefits of different target BP values during treatment. Current analyses indicate that **optimal reduction of the global CV risk is obtained by reducing BP below 140/90 mm Hg in most patients with hypertension, including those with concomitant IHD, previous MI, or stroke.** This major change in the approach to setting target BP in patients with high baseline CV risk that occurred in 2009 and was maintained in the present guidelines, is related, among others, to the existence of a phenomenon of the J curve, i.e. relatively higher CV risk with too low on-treatment BP values, which was observed in many large-scale clinical trials. In patients at high CV risk, however, BP should be reduced more rapidly to the target values.

There are two exceptions from the target BP given above. **In patients with diabetes, the recommended target BP values are below 140/85 mm Hg.** This conclusion results from multiple analyses showing the nadir of CV risk at these BP values in diabetic patients (based on the ACCORD, HOT, and INVEST studies). **In patients above 80 years of age, more cautious SBP reduction to values below 150 mm Hg is recommended,** based directly on the target SBP set in the HYVET trial which was the only successful study in this age group.

In patients with ISH, SBP should be reduced below 140 mm Hg but due to low DBP values, advanced age of most patients with this subtype of hypertension, and less

aggressive approach to treatment in the **elderly patients** with grade 1 hypertension, **attempts to reduce SBP to the target values should not lead to DBP reduction to very low values (< 65 mm Hg).**

4.1.3. Follow-up visits

Current practice indicates that in the initial treatment phase, when the diagnosis of hypertension is confirmed and treatment is initiated and intensified, follow-up visits should be set at monthly intervals, and after adequate BP control is obtained, their frequency may be reduced to once every 3 months. Intervals between follow-up visits should also depend on the degree of patient compliance, and the presence of target organ damage, concomitant disease, and other risk factors. The treatment plan should be adjusted to patient lifestyle and needs, with simplification of the therapy, reduction of the daily number of tablets taken by the patient, involving family members in the treatment process, and tailoring treatment to the financial situation of the patient.

4.2. Non-drug therapy

Non-drug therapy involves lifestyle changes that significantly reduce elevated BP, increase effectiveness of drug therapy, and probably may reduce the risk of CV events and prevent development of hypertension in those with a family history of hypertension. However, due to poor patient compliance regarding lifestyle changes, their formal recommendation should never delay initiation of drug therapy in high risk patients.

Non-drug therapy includes attaining normal body weight, appropriate diet with reduction of fat intake, particularly of saturated fats, and reduction of alcohol and salt intake, smoking cessation, and increasing regular physical activity.

4.2.1. Weight reduction and dietary recommendations

Reduction of excess body weight should be obtained by reduction of caloric intake and appropriate diet composition (Table 6). Patients are recommended to consume vegetables, low-fat dairy products, fibre, and protein from plant sources, and to limit their saturated fat and cholesterol intake. Intake of fresh fruits is also recommended, although caution should be exercised in overweight patients and those with diabetes due to high sugar content in fruits. A Mediterranean type diet is recommended, as is consumption of fish at least twice a week, and fruit and vegetable intake should be 300–400 g per day. In hypertensive patients, combining exercise with the Dietary Approaches to Stop Hypertension (DASH) study diet and weight reduction resulted in more pronounced BP and left ventricular mass reduction compared to the DASH diet only.

Available data, mostly from observational studies, do not indicate a higher risk of incident hypertension or higher BP values in persons who regularly consume coffee. In contrast, consumption of energy drinks and foods with high fructose content should be avoided.

Table 6. Basic dietary recommendations for hypertensive patients, aiming for body weight maintenance or reduction to normal values

Maintain daily caloric intake or reduce it in case of overweight or obesity
Increase intake of vegetables and other plant products (4–5 servings) rich in potassium, e.g. tomatoes (300 g/day)*
Avoid products with high animal fat content (saturated fatty acids and cholesterol)
Substitute fish, fruits, vegetables, and other products containing unsaturated fatty acids for fatty animal products

*Excluding patients with renal failure or increased risk of hyperkalaemia

Table 7. Recommendations regarding salt intake in hypertensive patients

Reduce salt intake from usual 9–12 g to about 5 g per day (85 mmol Na). To achieve this target:
— discontinue using salt when preparing meals at home and at the table
— eat meals prepared from fresh, natural products
— avoid products containing sodium compounds used as preservatives

Weight reduction, and particularly reduction of abdominal obesity, not only results in BP lowering but also reduces dyslipidaemia and insulin resistance. It has been estimated that reducing body weight by 10 kg contributes to SBP lowering by approximately 5–20 mm Hg, and this BP lowering effect is more pronounced in obese subjects compared to those with near-normal body weight.

4.2.2. Salt intake

A causal relationship has been proven between salt intake and BP values. Excessive salt intake may contribute to resistance to antihypertensive treatment.

Reduction of sodium intake to 75–100 mmol/day (4.35–5.8 g of salt) results in BP lowering by an average of 2–8 mm Hg. **Hypertensive patients should not consume more than 5 g of salt per day** (≤ 85 mmol of sodium) (Table 7). BP-lowering effect of reduction of sodium intake is seen in salt-sensitive subjects and is more pronounced in blacks, the elderly, and patients with diabetes, metabolic syndrome, and CKD. Limiting salt intake allows reduction of the number and doses of antihypertensive drugs. Evaluation of sodium intake should be based on measurements of 24-h urinary sodium excretion, although this approach may be prone to a significant error. Despite an inverse relationship between sodium excretion and total mortality found in the

Table 8. Recommendations regarding alcohol intake in hypertensive patients

Increased alcohol intake predisposes to increased stroke rates and attenuates the effect of antihypertensive drugs
Alcohol intake should be limited to:
— 20–30 g of pure ethanol daily in men
— 10–20 g of pure ethanol daily in women
Note: 10 g of pure ethanol corresponds to 250 mL of beer, 100 mL of wine, and 25 g of vodka

Table 9. Recommendations regarding smoking in hypertensive patients

Each patient should be asked about smoking at each visit
Active counselling should be undertaken regarding smoking cessation
Minimum anti-nicotine intervention should be performed at least once a year
If necessary, recommend:
— nicotine replacement therapy
— treatment with bupropione
— treatment with cytosine
— treatment with varenicline
If these measures fail, refer patients to addiction treatment centres
Weight gain should be prevented

Table 10. Basic recommendations regarding increased physical activity in hypertensive patients

Daily systematic exercise of moderate intensity for 30–45 min
Endurance exercises (walking, running, swimming) supplemented with resistance exercises (e.g., squatting), adjusted to age, concomitant conditions, and patient preferences
Avoidance of isometric exercises (lifting heavy weights)
In patients with cardiac disease, exercise electrocardiogram testing and medically supervised rehabilitation may be necessary

general population, no data are available to indicate that reducing large or moderate salt intake in hypertensives might be harmful. In addition, salt intake reduction in the TOHP study was associated with a lower risk of CV events.

4.2.3. Alcohol consumption

A linear relation is observed between alcohol intake and BP values. Increased alcohol consumption predisposes to more frequent occurrence of strokes and attenuates the effect of antihypertensive drugs. If total elimination of alcohol intake is not possible, it is recommended:

— **in men: daily alcohol consumption should be reduced to 20–30 g of pure ethanol;**

— **in women: daily alcohol consumption should be reduced to 10–20 g of pure ethanol.**

Total weekly alcohol consumption should not exceed 140 g in men and 80 g in women. The following amounts of alcoholic beverages contain 10 g of pure ethanol: 250 mL of beer, 100 mL of wine, and 25 g of vodka (Table 8).

4.2.4. Cigarette smoking

Smoking one cigarette induces a significant increase in BP and heart rate that persists for more than 15 min. Evidence is also available regarding harmful effects of passive smoking. In addition, smoking significantly increases the global risk of IHD, stroke, and peripheral arterial disease, particularly in hypertensive patients. Reducing smoking habit is an important component of CV risk reduction efforts in hypertensives (Table 9). Smoking status of the patient should be ascertained at each visit. Smokers should be counselled to quit. Medications to help quit smoking should be considered, including nicotine replacement therapy, buproprion, varenicline, and cytisine.

4.2.5. Physical activity

Appropriate physical activity is an important component of non-drug therapy. It has been shown that regular exercise may reduce BP by 4–9 mm Hg. An increase in physical activity also helps reduce overweight, increase general fitness, and reduce mortality. Patients with hypertension should be advised to engage in at least 30 min of moderate dynamic aerobic exercise, such as jogging, brisk walking, cycling, or swimming, on 5–7 days per week. Isometric exercises (to build up muscle strength without a dynamic component) are not recommended. Basic recommendations regarding increasing physical activity are summarised in Table 10.

4.3. Antihypertensive medications

The choice of antihypertensive medication(s) should take into account the effect of the drug(s) on other CV risk factors, the presence of subclinical target organ damage, CVD, and other concomitant disease, patient age and gender, possibility of drug interactions and adverse effects, medication cost and financial situation of the patient, and previous physician experience with a given therapy. Although the benefits of antihypertensive drug therapy in reducing mortality and the risk of CV events are largely dependent on BP lowering per se, some antihypertensive drug classes are categorised as major, and other drug classes do not have this status. The criterion underlying this distinction is the presence or absence of data from large clinical trials showing significant benefits of a given class in reducing mortality and the risk of CV events in patients with hypertension. In addition, the position taken in the previous PTNT guidelines was upheld that the results of large hypertension trials and their metaanalyses published in the recent years, including after 2011, along with pathophysiological clues and pharmacologic differences, suggest a possibility

of no class effect and/or better clinical utility of specific drugs within their classes, both major ones and others, in specific clinical situations, as indicated below when discussing drug classes, special patient populations, and individualisation of antihypertensive drug therapy.

4.3.1. Major drug classes

In uncomplicated hypertension, and in most cases of complicated hypertension and hypertension with concomitant diseases, except for hypertension in pregnancy, **antihypertensive therapy should be started with medications from the five major drug classes** with a proven beneficial effect on reducing CV mortality and/or the risk of CV events. **These are thiazide/thiazide-like diuretics, beta-blockers, calcium antagonists, angiotensin-converting enzyme inhibitors (ACEI), and angiotensin II (AT_1) receptor blockers or sartans (ARB, angiotensin receptor blockers).** In accordance with the above mentioned position regarding within-class differences between drugs, we continue to prefer certain subgroups within some major antihypertensive drug classes (Table 11).

4.3.1.1. Thiazide/thiazide-like diuretics

Thiazide/thiazide-like diuretics are among first-line drugs used as monotherapy, particularly in the elderly patients, subjects above 80 years of age (indapamide), and patients with a history of stroke. They are also often used as a part of two-drug combinations, particularly in patients with concomitant diabetes, those with renal dysfunction or with coexisting symptomatic HF, and are a necessary component of three-drug combinations in the treatment of more severe hypertension. Of note, full BP-lowering effect of thiazide/thiazide-like diuretics is seen only after several days of treatment. In the recent years, some data have been published indicating that thiazide-like diuretics (chlorthalidone, indapamide) should be preferred due to more evidence of benefit regarding CV risk prevention in large-scale clinical trials (ALLHAT, ADVANCE, HYVET, PATS), low utility of hydrochlorothiazide monotherapy in currently used low doses of 12.5–25 mg (smaller and shorter-lasting BP-lowering effect), and a more beneficial metabolic profile of thiazide-like diuretics, although the most recent metaanalysis did not confirm the latter difference. The two thiazide-like diuretics mentioned above provide a choice based on the expected diuretic effect, ranging from moderate (indapamide) to large (chlorthalidone). Attention should be paid to possible metabolic (dyslipidaemia and the risk of new-onset diabetes) and electrolyte disturbances (hypokalaemia, hyperuricaemia, and hyponatremia), and respective laboratory parameters should be monitored during long-term therapy with conventional thiazide and thiazide-like diuretics due to the fact that an association was observed between long-term benefits of these drugs and the occurrence of the above mentioned disturbances during treatment.

Table 11. Major classes of antihypertensive drugs

Five major classes of antihypertensive drugs
With proven outcome benefits
Used as monotherapy
Recommended for combination treatment
Thiazide diuretics (preferred thiazide-like agents)
Beta-blockers (preferred vasodilatatory agents)
Calcium antagonists (preferred dihydropyridines)
Angiotensin-converting enzyme inhibitors
Angiotensin receptor blockers

Potassium supplementation is often necessary during treatment with thiazide/thiazide-like diuretics.

4.3.1.2. Beta-adrenergic receptor blockers

Use of beta-blockers in the treatment of hypertension is recommended in patients with tachycardia and/or arrhythmia, evidence of a hyperkinetic circulation, particularly in younger subjects, and with concomitant HF or coronary artery disease, particularly after a previous MI. Following oral administration, BP-lowering effect of beta-blockers is seen within several hours but the full treatment effect is evident only after several weeks. In the recent years, multiple controversies arose regarding use of beta-blockers, in particular of older generations, as monotherapy in patients with hypertension, and thus whether beta-blockers should remain among the first-line drugs for the treatment of hypertension. In several large-scale clinical trials in hypertensives, conventional cardioselective beta-blockers (atenolol) were less effective in preventing CV events compared to inhibitors of the renin–angiotensin–aldosterone system (RAAS) and calcium antagonists. Metaanalyses of clinical trials showed a lower efficacy of these drugs in inducing regression of left ventricular hypertrophy and preventing stroke, which may be related to their weaker effect on central aortic pressure. However, other metaanalyses showed benefits of conventional cardioselective beta-blockers in the treatment of hypertension in patients after an acute coronary syndrome, and mortality benefits in hypertensive patients with chronic obstructive pulmonary disease (COPD) and heart disease.

The position taken in the previous PTNT guidelines was upheld that vasodilating agents (carvedilol, nebivolol) should be preferred among beta-blockers in patients with uncomplicated hypertension. This has been reflected in the text of the 2013 ESH/ESC guidelines that noted some beneficial aspects of the mechanism of action of vasodilating beta-blockers. Due to their haemodynamic properties (smaller negative chronotropic effect and a reduction of total peripheral resistance), resulting in a more favourable effect on central aortic pressure, these drugs should be preferred in uncomplicated hypertension if a beta-blocker is indicated.

However, appropriate clinical studies would be required to document the efficacy of vasodilating beta-blockers in the prevention of CV events in hypertensive patients. Additional receptor-mediated effects (alpha$_1$-adrenergic receptor blockade by carvedilol, beta$_3$-adrenergic receptor activation by nebivolol), beneficial effects on metabolic parameters and endothelial function, and the results of large-scale clinical trials (GEMINI, COMET, SENIORS) all suggest that vasodilating beta-blockers should be preferred if a beta-blocker is indicated in hypertensives with diabetes or metabolic syndrome, and in those after CV events and with coexisting CVD. If it is necessary to achieve desired heart rate reduction (due to coexisting HF, IHD, or aortic dissection), conventional, highly cardioselective beta-blockers (bisoprolol, betaxolol, metoprolol succinate) may be more useful.

4.3.1.3. Calcium antagonists

An important advantage of calcium antagonists is their neutral metabolic effect, and thus these drugs are useful in combination with RAAS inhibitors in patients with concomitant lipid and/or carbohydrate metabolism disturbances. Dihydropyridines should be preferred as monotherapy, as much more evidence from large-scale clinical trials (ALLHAT, ASCOT, VALUE, ACCOMPLISH) is available for this subgroup. Of note, efficacy and safety of long-acting dihydropyridines were shown in the elderly, including patients with ISH (Syst-Eur), patients with peripheral arterial disease, and those with concomitant COPD or asthma. Some metaanalyses suggest high efficacy of calcium antagonists in the prevention of atherosclerosis, and clinically in the prevention of stroke, but this was not confirmed in secondary stroke prevention studies. On the other hand, metaanalyses also indicate that these drugs are less effective in preventing HF and reducing proteinuria. Although most evidence for CV risk reduction in large-scale clinical trials was obtained for amlodipine, use of this drug is associated with a relatively high rate of leg oedema and thus lercanidipine and lacidipine are alternative long-acting but better tolerated drugs of this class.

4.3.1.4. Angiotensin-converting enzyme inhibitors and angiotensin receptor blockers

Both these classes of RAAS inhibitors are among the most commonly used in the treatment of hypertension and have most indications in special patient populations.

ACEI are preferred in hypertension with target organ damage or high CV risk, particularly with coexisting IHD, HF or renal disease, in hypertension with metabolic syndrome and/or diabetes, and, in combination with a thiazide-like diuretic, in patients with a history of stroke. Metaanalyses suggest additional benefits of ACEI in the prevention of cardiac events beyond BP lowering effect that may be associated with bradykinin-mediated effects of these drugs, particularly those with high tissue affinity, such as perindopril (EUROPA study). In the SMILE-4 study, sulfhydryl (-SH) group-containing zofenopril was more effective compared to ramipril in patients with post-infarction left ventricular dysfunction, particularly those with hypertension.

ARB are preferred in patients with hypertension and left ventricular hypertrophy, concomitant renal disease (including diabetic nephropathy), and in those with a history of stroke, while in hypertensives with IHD or HF they are recommended as an alternative to ACEI if the latter are not tolerated. Some metaanalyses suggested that ARB prevent stroke better than MI.

The 2013 ESH/ESC guidelines questioned the clinical importance of previous suggestions regarding differences between ACEI and ARB in regard to CV event prevention, based on a large 2009 metaanalysis and the ONTARGET study which directly compared the effect of ramipril and telmisartan on CV mortality and morbidity in high CV risk patients and showed no difference between these two drugs. However, three important metaanalyses were published in 2012–2014, focusing on different patient populations, i.e. hypertensives, patients with hypertension and/or IHD, and diabetic patients, that all showed an advantage of ACEI over ARB. The first of these metaanalyses suggested a special position of perindopril among ACEI, particularly during combination therapy. Taking into account consistent results of these metaanalyses, it seems reasonable to conclude that ACEI should be preferred over ARB (with indications retained for telmisartan) in patients with hypertension and high CV risk, i.e., with concomitant CV and metabolic complications, a position which has been reflected in the table that summarises individualisation of antihypertensive drug therapy. In contrast, ACEI and ARB have equivalent positions in uncomplicated hypertension with lower CV risk.

4.3.2. Other antihypertensive drugs

Due to lack of prospective studies evaluating the effect on mortality and CV risk, other drug classes, such as alpha-blockers, aldosterone antagonists, loop diuretics, imidazoline receptor agonists, and peripheral and central sympatholytic drugs, are not recommended as first- and second-line antihypertensive medications. However, this does not preclude use of these drugs during combination therapy if indicated individually, and in resistant hypertension, usually as fourth- and fifth-line drugs.

Similarly to major antihypertensive drug classes, pathophysiological data, pharmacokinetic differences, and varying severity of adverse effects suggest better clinical utility of specific drugs also within other groups of antihypertensive medications (Table 12). This is particularly the case for the preference of torasemide over furosemide among loop diuretics (due to more favourable pharmacokinetics), and eplerenone over spironolactone (less adverse effects) among aldosterone antagonists, although eplerenone is not licensed to treat uncomplicated hypertension in Poland. In patients with

Table 12. Other drug classes useful in the treatment of hypertension

Loop diuretics (torasemide)
Alpha-blockers (doxazosin)
Aldosterone antagonists (eplerenone)
Central sympatholytic agents (clonidine)
Imidazoline receptor antagonists (rilmenidine)
Peripheral sympatholytic agents (methyldopa)

concomitant benign prostatic hyperplasia, uroselective tamsulosin should be rather used if hypertension requires one- or two-drug therapy, while resistant hypertension would require doxazosin as this alpha-blocker exerts a BP-lowering effect.

4.4. Drug treatment algorithm

Antihypertensive drug therapy is initiated using one (monotherapy) or two (combined therapy) drugs chosen from major drug classes. Figure 3 shows the algorithm for the management of hypertension, and in particular the decision to initiate treatment with monotherapy or combined therapy depending on the severity of hypertension and the degree of BP lowering necessary to reach target BP. As target BP values have been unified, the algorithm continues not to include CV risk related to concomitant metabolic disturbances or CV and renal complications as a criterion for the choice between monotherapy and combined therapy.

4.4.1. Monotherapy

In monotherapy, most currently used antihypertensive medications lower BP by less than 20/10 mm Hg and such an effect is observed in only about 50–60% of patients. Thus, **therapy is initiated with one drug only in grade 1 hypertension.** It should be remembered that treatment benefits are mostly related to BP lowering, and thus medications characterised by a high trough-to-peak (T/P) ratio are preferred, particularly during monotherapy, as they provide better 24-h BP control and may be given once daily which improves patient compliance.

Patient's age may serve as a pathophysiological clue regarding the initial drug choice in uncomplicated hypertension. RAAS inhibitors and beta-blockers may be effective in younger patients, in whom so called resistance or high-renin hypertension is often present, and thiazide/thiazide-like diuretics and calcium antagonists in older patients, who are more frequently characterised by volume or low-renin hypertension. Patient gender may also be factor, as RAAS inhibitors should be avoided in women of reproductive years, and beta-blockers or calcium antagonist should be preferred instead.

Increasing the drug dose to the maximum dose exerts little additional BP lowering effect but largely increases the risk of adverse effects. Thus, if monotherapy using a standard drug dose does not produce the desired effect, adding a second drug has been considered the optimal next step among possible options.

4.4.2. Combined therapy

Most patients with hypertension require two-drug therapy for appropriate BP control. This is the case in half of patients with grade 1 hypertension and in most patients with higher baseline BP values. Thus, **therapy is initiated with two drugs in grade 2 and 3 hypertension,** with an option of increasing the dose of one or both drugs to the maximum dose.

Major two-drug combinations used in the treatment of hypertension, which are well tolerated, effectively lower BP, and reduce CV risk, include:

- **ACEI + calcium antagonist;**
- **ACEI + thiazide/thiazide-like diuretic;**

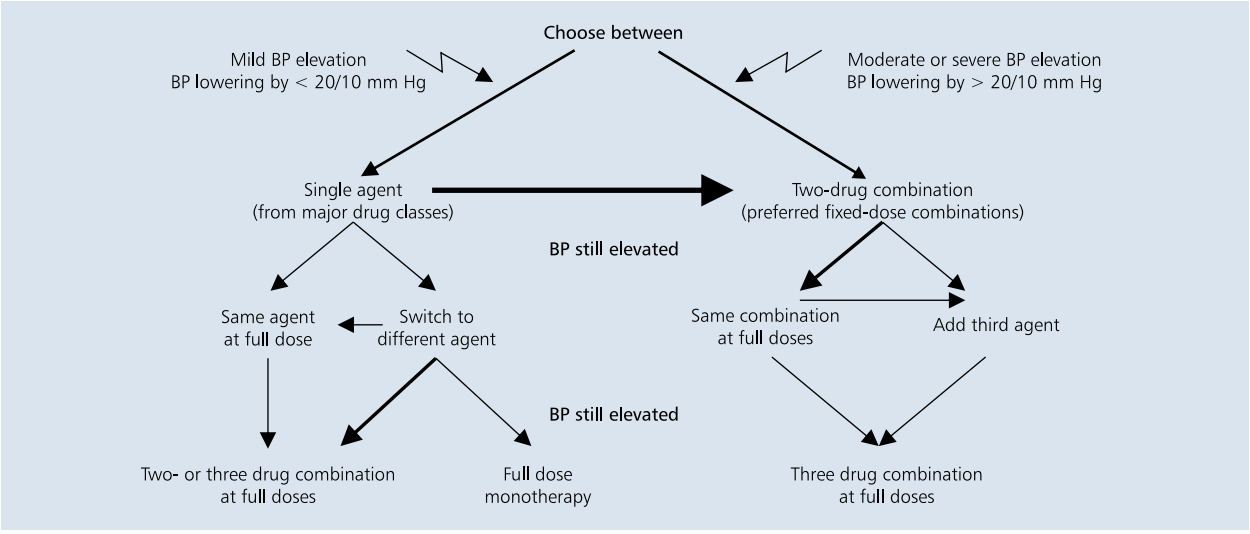

Figure 3. Management algorithm for antihypertensive drug therapy; BP — blood pressure

— **ARB + thiazide/thiazide-like diuretic;**
— **ARB + calcium antagonist;**
— **ACEI + beta-blocker;**
— **calcium antagonist + beta-blocker;**
— **calcium antagonist + thiazide/thiazide-like diuretic.**

Inclusion of the last two combinations among the preferred two-drug combinations in the current guidelines is related to the fact of their practical use in two important patient groups: **the elderly (calcium antagonist + thiazide/ /thiazide-like diuretic)**, which was also reflected in the 2013 ESH/ESC guidelines, and **young/middle-aged women (beta-blocker + dihydropyridine calcium antagonist)** in whom RAAS inhibitors should be avoided.

In patients with **hypertension and cardiac disease** (IHD, HF), the preferred combination of **ACEI and beta-blocker** is commonly used. It is the only preferred two-drug combination without available fixed-dose combination drug products.

In the current guidelines, the combination of **beta-blocker and thiazide diuretic** has been considered **acceptable** due to multiple trials that documented its benefits vs. placebo in the early era of evidence-based medicine, as also reflected in the 2013 ESH/ESC guidelines. It should be remembered, however, that such combinations are generally less effective in reducing CV risk (ASCOT and LIFE studies) and may be associated with a higher risk of metabolic disturbances and new-onset diabetes, although this risk is mitigated if the combination involves a thiazide-like diuretic and/or a vasodilating beta-blocker.

Note: RAAS inhibitors should be very cautiously combined with potassium-sparing diuretics as this may lead to hyperkalaemia. The combination of **ACEI and ARB is not recommended** due to an increased risk of adverse renal effects without additional benefits, as confirmed in the recent metaanalyses. Non-dihydropyridine calcium antagonists (verapamil and diltiazem) combined with beta-blockers predispose to bradycardia and HF, and diuretics combined with alpha-blockers predispose to orthostatic hypotension. The preferred two-drug combinations in the treatment of hypertension are summarised in Figure 4.

About 30% of patients require at least three drugs for adequate BP control. **In uncomplicated hypertension, the basic three-drug combination includes a RAAS inhibitor, a calcium antagonist, and a thiazide/thiazide-like diuretic.**

When selecting antihypertensive drugs for combination therapy, the major criterion should be an increase of their therapeutic effect with improved treatment tolerance.

4.4.3. Fixed-dose combinations of antihypertensive drugs

Combined therapy benefits from the use of fixed-dose combinations of antihypertensive drugs, as this increases treatment effectiveness (STITCH and ACCOMPLISH studies), simplifies the treatment scheme, and increases patient compliance (metaanalyses). In addition, the use of fixed-dose combinations

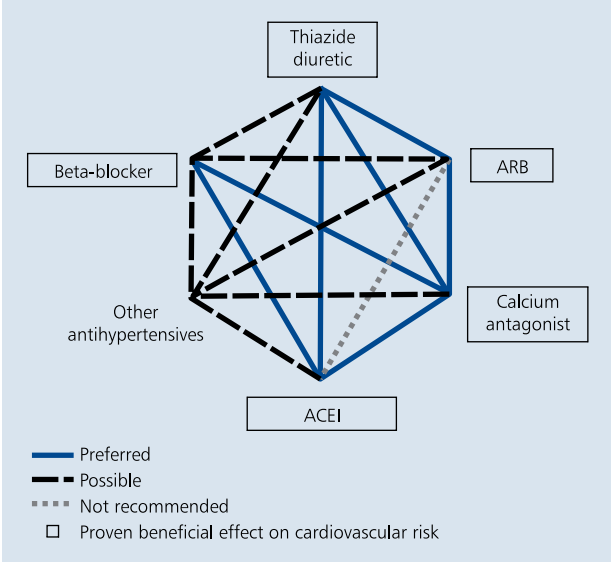

Figure 4. Two-drug combinations of antihypertensive drugs; ACEI — angiotensin-converting enzyme inhibitor; ARB — angiotensin receptor blocker

is associated with an increased antihypertensive efficacy compared to the algorithm of monotherapy-combined treatment, while use of lower doses minimises the risk of dose-related adverse effects. Fixed-dose combinations are recommended to initiate antihypertensive drug therapy in patients with grade 2 hypertension, as reflected in the management algorithm. Among the seven listed preferred two-drug combinations, six are available in Poland as fixed-dose combination drug products. Our decision to supplement the basic combinations of a RAAS inhibitor with a calcium antagonist or a thiazide/thiazide-like diuretic with two others (thiazide/thiazide-like diuretic + calcium antagonist and beta-blocker + dihydropyridine calcium antagonist) was related, among other factors, to the introduction of such fixed-dose combinations in Poland (indapamide + amlodipine and bisoprolol + amlodipine).

An interesting addition to the armamentarium of fixed-dose combination drug products in Poland has been the introduction of three-drug fixed-dose combinations, offering the possibility of single tablet therapy also in patients with higher baseline BP values, including those with grade 3 hypertension. Both available three-drug fixed-dose combinations (ACEI + dihydropyridine calcium antagonist + thiazide-like diuretic and ARB + dihydropyridine calcium antagonist + thiazide-like diuretic) fulfil the criteria of an optimal drug combination in uncomplicated hypertension. Of note, analyses of randomised studies indicate potential benefits in terms of CV risk reduction for the available three-drug combination of perindopril + indapamide + amlodipine.

In the future, combined therapy using doses lower than standard ones available in two-and three-drug fixed-dose combinations may prove to be an alternative approach to

initiating antihypertensive therapy in patients with grade 1 and grade 2/3 hypertension, respectively.

4.4.4. Chronotherapy of hypertension

Studies based on ABPM indicate that in many patients, additional CV risk is associated with masked nocturnal hypertension, non-dipping BP pattern, or excessive morning BP surge. Typical morning dosing of long-acting antihypertensive drugs may not correct these disturbances of the circadian BP profile. In these circumstances, particularly with the non-dipping BP pattern or masked nocturnal hypertension, modification of the timing of antihypertensive drug administration should be considered, with evening drug dosing (Fig. 5). As this approach to chronotherapy of hypertension, first suggested in the 2011 PTNT guidelines, has become popular in Poland, it should be noted that evening dosing of antihypertensive drugs must be based on evaluation by ABPM (non-dipping pattern) and rather involve dosing of RAAS inhibitors. Evening dosing of ARB or ACEI (with a preference given rather to shorter-acting drugs and those tested in chronotherapy studies, e.g. ramipril and valsartan) was associated with an improved circadian BP pattern, reduced microalbuminuria, and proved safe in large-scale clinical trials (HOPE, Syst-Eur). Unless nocturnal hypertension is found, evening dosing of antihypertensive drugs is contraindicated in patients with glaucoma.

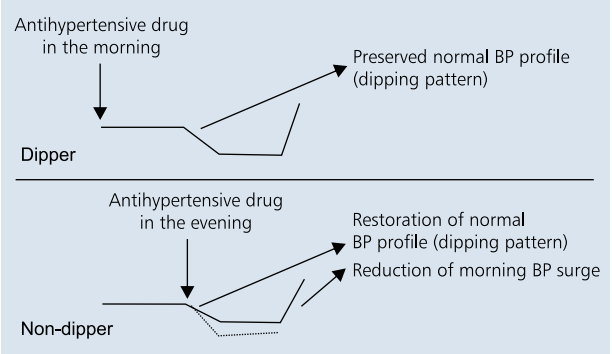

Figure 5. Suggested timing of antihypertensive drug administration in relation to the 24-h blood pressure (BP) profile

Table 13. Individualisation of drug therapy

When choosing (or avoiding) any particular drug (or drug combination), the following should be taken into consideration:
Presence of cardiovascular and renal disease
Presence of other concomitant conditions
Presence of other cardiovascular risk factors and target organ damage
Demographic factors (age, gender, race, body weight)
24-h blood pressure-lowering efficacy of a drug
Drug adverse effect profile
Drug cost — but never at the price of lower treatment effectiveness and tolerance
Previous physician and patient experience with a given drug (drugs)

5. SPECIAL PATIENT POPULATIONS

The approach to drug therapy adopted in the current and previous guidelines gives much emphasis to its individualisation (Tables 13, 14).

The choice of first-line therapy is important due to potential benefits beyond BP lowering documented in large-scale clinical trials for specific types of CV and renal events and metabolic disturbances in hypertension, or a possibility to obtain additional benefits or avoid adverse effects in case of concomitant diseases. Due to widespread use of combination therapy, recommendations regarding individualisation of antihypertensive drug therapy also extend to second-line drugs in specific clinical scenarios. Specific indications for and contraindications to different drug classes are shown in Tables 14 and 15, and indications for the use of different drug combinations or fixed-dose combination drug products are shown in Figure 6.

5.1. Hypertension in the elderly

Large clinical trials and metaanalyses indicate that antihypertensive therapy in patients above 65 years of age significantly reduces the rate of strokes, HF incidence, and CV mortality. Patients with SBP ≥ 160 mm Hg were recruited to these studies, and SBP was lowered below 150 mm Hg but not below 140 mm Hg. Thus, antihypertensive therapy may be clearly recommended in the elderly patients with grade 2 hypertension, in whom SBP should be lowered to 140–150 mm Hg. However, due to rational reasons and the fact that persons above 65 years of age constituted a significant proportion of patients in many clinical trials, antihypertensive therapy should also be considered in those with SBP above 140 mm Hg, aiming for target SBP below 140 mm Hg, if the patient is in a good overall condition and tolerates the therapy well. In patients above 80 years of age, based on the results of the HYVET study, it may be generally recommended to initiate antihypertensive therapy if SBP is above 160 mm Hg, aiming for target SBP below 150 mm Hg. However, due to differences in the general health condition of these individuals, the decision to initiate therapy should be individualised, and BP lowering should be gradual and carefully monitored by the physician. In the elderly patients with concomitant disease, such as coronary artery disease, CKD or diabetes, specific target BP values accepted for these clinical conditions should apply.

Benefits of antihypertensive therapy in the elderly are comparable to those obtained in younger age groups. However, due to a reduced adaptive capacity of the CV system and the risk of orthostatic hypotension, therapy should be more cautious, and target BP values should be reached more gradually. Due to the risk of orthostatic hypotension and falls, BP in the elderly hypertensive should be measured after 1 and 3 min of standing (orthostatic testing) in the following situations:

Table 14. Preferred first (I) and second (II) choice antihypertensive drug classes in specific conditions

Clinical condition	Preferred first and second choice drugs								
	DT	BB	CA-dhp	CA-ndhp	ACEI	ARB	AA	LD	MD
Left ventricular hypertrophy					I	I			
Ischaemic heart disease		I	II A	II B	I 1	II C 2	II D		
Heart failure	II	I 3			I	II C 4	II	II	
Permanent atrial fibrillation		I	I						
Tachyarrhythmias		I							
Aortic dissection		I							
Peripheral arterial disease			I		I				
Previous stroke	I 5				II	I			
Metabolic syndrome			II	II	I	I			
Diabetes	II 5		II		I	I			
High-risk patients (multiple cardiovascular and metabolic complications)					I 6	II C 7			
Gout			II		I	I B			
Hypertension in the elderly	I		I		II	II			
Hypertension above 80 years of age	I 9				II				
Isolated systolic hypertension	I		I		II	II			
Albuminuria/proteinuria			II	II	I	I			
Diabetic/non-diabetic nephropathy					I	I			
Chronic kidney disease					I	I		II	
Pregnancy		II 10	II 11	II 12					I
Erectile dysfunction		II 13	II		I	I			
Asthma/chronic obstructive pulmonary disease			I			I			
Glaucoma		I							

I — first choice drug; II — second choice drug
A — with angina; B — with beta-blocker intolerance; C — with ACEI intolerance; D — after myocardial infarction
1 — preferred agents: perindopril, ramipril, zofenopril; 2 — preferred agents: telmisartan and valsartan; 3 — only carvedilol, bisoprolol, metoprolol XR/CR, nebivolol; 4 — preferred agents: candesartan and valsartan; 5 — preferred agent: indapamide; 6 — preferred agents: perindopril, ramipril; 7 — telmisartan has the first-choice status; 8 — preferred agent: losartan; 9 — only indapamide; 10 — preferred agent: labetalol (poor availability in Poland), of other beta-blockers only metoprolol; 11 — only nifedipine (extended release preparation preferred); 12 — only verapamil; 13 — only nebivolol
DT — thiazide/thiazide-like diuretics; BB — beta-blockers; CA-dhp — dihydropyridine calcium antagonists; CA-ndhp — non-dihydropyridine calcium antagonists; ACEI — angiotensin-converting enzyme inhibitors; ARB — angiotensin receptor blockers; AA — aldosterone antagonists; LD — loop diuretics; MD — methyldopa

— therapy initiation;
— treatment change;
— history of falls;
— dizziness or near-fainting;
— concomitant diabetes.

Although the basic principles of non-drug therapy in the elderly hypertensives are the same as in younger subjects, limitations due to impaired mobility and reduced fitness, precluding regular exercise, should be borne in mind.

All major classes of antihypertensive medications were tested in large-scale clinical trials in the elderly patients, and recent metaanalyses do not indicate any differences in the efficacy of antihypertensive medications in relation to the patient's age. However, as dictated by the clinical experience, and if there are no specific indications to individualise therapy otherwise, first-line drugs are thiazide/thiazide-like diuretics and dihydropyridine calcium antagonists or their combination. In clinical trials in patients with the most common type of hypertension in the elderly, ISH, only diuretics and calcium antagonists with a possible addition of a RAAS inhibitor were used. In patients above 80 years of age, available studies (HYVET) indicate that the therapy should be initiated with a long-acting thiazide-like diuretic (indapamid), with a possible addition of an ACEI (Table 16).

5.2. Hypertension in women

In the Blood Pressure Lowering Treatment Trialists' Collaboration metaanalysis that compared benefits of antihypertensive therapy in men and women, both similar BP-lowering effect and similar treatment outcomes were noted in both genders,

Table 15. Absolute and relative contraindications to specific antihypertensive drug classes

Drug class	Absolute contraindications	Relative contraindications
Diuretics	Gout (thiazides)	Metabolic syndrome
		Glucose intolerance
		Hyponatremia < 130 mmol/L
		Pregnancy
Beta-blockers	Asthma	Chronic obstructive pulmonary disease
	Grade 2 or 3 AVB	Metabolic syndrome
		Glucose intolerance
		Athletes and physically active patients
Dihydropyridine calcium antagonists		Tachyarrhythmias
		Heart failure
Non-dihydropyridine calcium antagonists (verapamil/diltiazem)	Grade 2 or 3 AVB	Chronic constipation (verapamil)
	Heart failure	
	Bradycardia < 50 bpm	
Angiotensin-converting enzyme inhibitors	Pregnancy	
	Hyperkalaemia > 5.0 mmol/L	
	Bilateral or single kidney renal artery stenosis	
	Transplant renal artery stenosis	
	History of angioneurotic oedema	
Angiotensin receptor blockers	Pregnancy	
	Hyperkalaemia > 5.0 mmol/L	
	Bilateral or single kidney renal artery stenosis	
Aldosterone antagonists	Transplant renal artery stenosis	
	Chronic kidney disease (eGFR < 30 mL/min)	
	Hyperkalaemia > 5.0 mmol/L	
	Pregnancy	

AVB — atrioventricular block; eGFR — estimated glomerular filtration rate

with no differences in response to different class of antihypertensive medications. In women who plan pregnancy or are potentially able to conceive, use of ACEI and ARB should be avoided due to potential teratogenic effects of these drugs.

Hypertension is not an absolute contraindication for the use of hormonal replacement therapy or oral contraception. If these therapies are used, BP should be measured at each visit and hypertension should be treated according to the general management principles.

The likelihood of BP increase in hypertensive women who receive hormonal replacement therapy during menopause is small, but hormonal replacement therapy and selective oestrogen receptor modulators should not be use for primary or secondary prevention of CV events.

Use of oral contraceptives is associated with a small but significant BP increase and development of hypertension. However, most studies evaluated the effect of older generation contraceptives that contained a higher oestrogen dose than those currently used. Data are lacking regarding the effect of newer hormonal contraceptive methods (vaginal and transdermal) on BP but an association was confirmed between newer contraceptive methods and an increased risk of venous thrombosis. Progestin-only containing oral contraceptives (minipills) are not considered contraindicated in mild and moderate hypertension but they constitute a minor proportion of currently used oral contraceptives.

5.3. Hypertension in pregnant women

There are two major types of hypertension in pregnancy:

- **chronic (preexisting) hypertension —** BP ≥ 140/90 mm Hg before pregnancy or developing before 20 weeks of gestation and persisting beyond 12 weeks after delivery;
- **gestational (pregnancy-induced) hypertension** — developing after 20 weeks of gestation and resolving within 12 weeks after delivery.

Preeclampsia is a multiorgan dysfunction syndrome complicating hypertension in pregnancy, with a serious prognosis for the pregnancy itself and future CV risk of the woman. It usually develops between 20 weeks of gestation and 3 days after delivery, with worse pregnancy outcomes if it occurs early, particularly before 32 weeks of gestation. It is defined as:

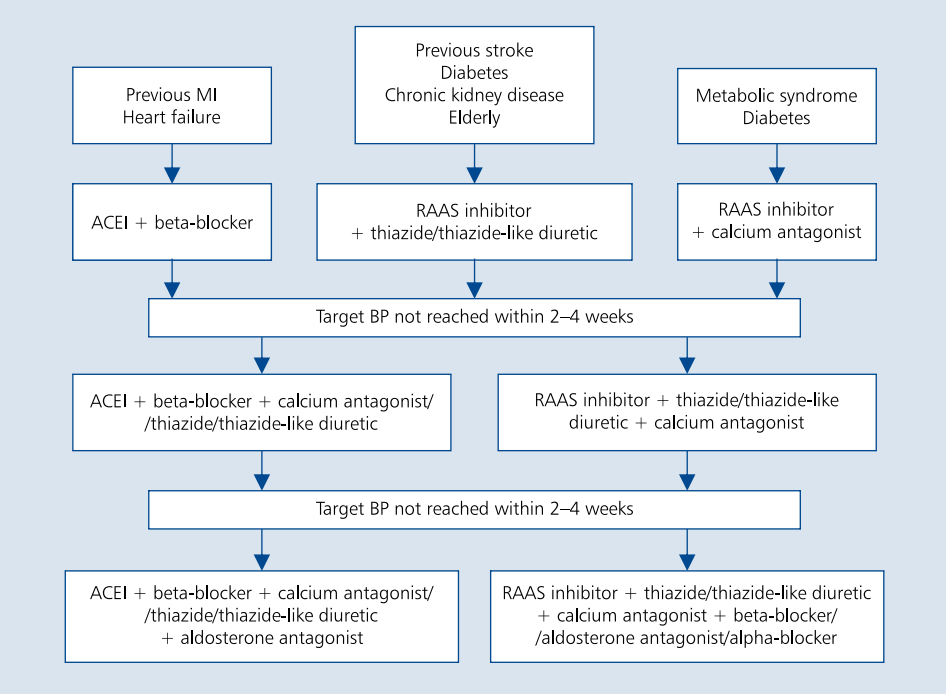

Figure 6. Preferred choices of combined therapy/fixed-dose combination products and intensification of antihypertensive drug therapy in relation to concomitant conditions; ACEI — angiotensin-converting enzyme inhibitor; BP — blood pressure; MI — myocardial infarction; RAAS — renin–angiotensin–aldosterone system

Table 16. Antihypertensive treatment strategies in the elderly

Drug therapy to reduce SBP to between 150 and 140 mm Hg is recommended in patients aged 65–80 years with grade 2–3 hypertension
In patients > 80 years with grade 2–3 hypertension, drug therapy to reduce SBP to between 150 and 140 mm Hg is recommended, provided the patient is in a good physical and mental condition
In patients aged 65–80 years with grade 1 hypertension, drug therapy with a target SBP < 140 mm Hg may be considered if the treatment is well tolerated
In patients who reach 80 years of age, continuation of previous antihypertensive therapy may be considered regardless of on-treatment blood pressure values
In patients > 80 years with grade 1 hypertension, drug therapy is not recommended
In the elderly, initial drug doses should be lower, and subsequent therapy intensification should be more cautious due to a higher risk of adverse effects (hypotension)
Due to a reduced intellectual capacity of the elderly, treatment should be simplified, with frequent use of fixed-dose combination drug products
All major drug classes may be used, with some preference of thiazide/thiazide-like diuretics and dihydropyridine calcium antagonists, and therapy intensification using a RAAS inhibitor
In the elderly with isolated systolic hypertension, thiazide/thiazide-like diuretics and dihydropyridine calcium antagonists are preferred
In patients > 80 years, the preferred first line drug is indapamide, and the second line drug is ACEI

ACEI — angiotensin-converting enzyme inhibitor; RAAS — renin–angiotensin–aldosterone system; SBP — systolic blood pressure

— **gestational (pregnancy-induced hypertension)** — new-onset BP ≥ 140/90 mm Hg (mean of ≥ 2 measurements within ≥ 4 h, and if BP ≥ 160/110 mm Hg — within minutes); and
— any of the following findings occurring de novo: proteinuria (≥ 300 mg/24 h, protein/creatinine ratio ≥ 0.3, protein 1+ or more on reagent strip), low platelet count (< 100,000/μL), renal function worsening (serum creatinine > 1.1 mg/dL or doubling of the serum creatinine level in CKD), hepatic dysfunction (increase in alanine transaminase/aspartate transaminase level to two times the upper limit of normal), pulmonary oedema, central nervous system signs or symptoms, vision disturbances.

Preeclampsia is likely related to placental dysfunction and thus develops mostly in the second half of pregnancy in pregnancy-induced hypertension but may also occur in

Table 17. Antihypertensive treatment strategies in pregnant women

In all pregnant women, modified non-drug treatment is recommended (no alcohol intake and smoking, limitation of physical activity), without limitation of salt intake
Drug treatment is recommended if BP is ≥ 150/95 mm Hg in pregnant women with uncomplicated and asymptomatic preexisting hypertension, and ≥ 140/90 mm Hg in women with pregnancy-induced hypertension (regardless of the presence of proteinuria), and complicated, symptomatic, or secondary preexisting hypertension
Target BP in pregnant women is < 140/90 mm Hg. Frequent evaluation by ABPM is recommended
BP values ≥ 170/110 mm Hg should be considered an indication for hospital admission
In pregnant women with hypertension, the preferred drug is methyldopa. Labetalol* may be added in the first trimester, and metoprolol tartrate and/or calcium antagonist (nitrendipine or nifedipine SR* or verapamil) may be added starting from the second trimester
Hydralazine* may be considered as a fourth-line drug. Continuation of pre-pregnancy treatment with a thiazide diuretic is controversial (harmful effects of hypovolaemia in preeclampsia and an increased risk of schizophrenia in children)
In severe hypertension that cannot be controlled by oral drugs, nitroglycerin by intravenous infusion, intravenous labetalol, or intravenous urapidil may be used. Seizure prevention is also necessary using intravenous magnesium sulphate that also has a BP-lowering effect
The following drugs are absolutely contraindicated during pregnancy and breastfeeding due to observed or potential teratogenic effects: ACEI, ARB, renin inhibitors, aldosterone antagonists, and diltiazem
All antihypertensive drugs are secreted to breast milk, and thus the same drugs are recommended during lactation as during pregnancy
Hypertension is an indication for acetylsalicylic acid 75–150 mg daily starting from 12 weeks of gestation until delivery to prevent preeclampsia

*Drugs not routinely available in Poland, may be imported individually by a physician prescription
ABPM — ambulatory blood pressure monitoring; ACEI — angiotensin-converting enzyme inhibitors; ARB — angiotensin receptor blockers; BP — blood pressure

women with preexisting hypertension, in whom BP elevation with other features of preeclampsia is seen after 20 weeks of gestation — this is diagnosed as **preeclampsia superimposed upon chronic hypertension**.

If hypertension was first found after 20 weeks of gestation, without other evidence of preeclampsia, and previous BP values are unknown or uncertain, **antenatally unclassified hypertension** should be diagnosed and the diagnosis should be verified at or beyond 12 weeks after delivery.

Other serious complications of hypertension in pregnancy include the **HELLP syndrome** (clotting abnormalities, hepatic dysfunction, and low platelet count) and **eclampsia**, or symptoms of central nervous system dysfunction.

Is secondary hypertension (renal artery stenosis or phaeochromocytoma) is suspected in a pregnant woman, appropriate investigations and treatment should be undertaken before the third trimester, and the optimal approach would to be to perform full diagnostic work-up for secondary hypertension before pregnancy.

The principles of antihypertensive treatment in pregnant women are summarised in Table 17.

5.4. Hypertension in patients with metabolic syndrome

Hypertension or high normal BP is a frequent component of metabolic syndrome. Recommending lifestyle changes, particularly body weight reduction and increased physical activity, is very important in all individuals with metabolic syndrome as the first and foremost intervention in the management of hypertension. The aim is to reduce body weight by 7–10% over 6–12 months by modest reduction of caloric intake (by 500–1000 kcal per day) which is usually more effective than a more rigorous diet.

Antihypertensive drug therapy is recommended for BP ≥ 140/90 mm Hg, with the aim to lower BP below 140/90 mm Hg. Currently, no evidence from outcome trials justifies initiation of drug treatment in patients with metabolic syndrome and high normal BP. Metabolic syndrome is associated with a high risk of developing diabetes, and thus the effect of antihypertensive drugs on glucose metabolism should be taken into consideration when choosing between drug classes. Drug therapy should be initiated with RAAS inhibitors which delay development of diabetes, with the addition of a calcium antagonist if necessary. Beta-blockers and conventional thiazide diuretics should be avoided in patients with metabolic syndrome. If drugs from these classes are indicated, vasodilating beta-blockers and thiazide-like diuretics should be chosen. When prescribing a diuretic, a potassium-sparing preparation should be considered, as hypokalaemia worsens glucose tolerance.

5.5. Hypertension in diabetic patients

The prevalence of hypertension among diabetic patients is increased compared to the general population. Nighttime hypertension is common and often masked. Thus, ABPM is recommended in each diabetic patient.

BP should also be measured in the standing position in case of symptoms suggesting hypotension during therapy intensification.

In patients with hypertension and diabetes, antihypertensive drug therapy is typically recommended when BP is above

140/90 mm Hg. No evidence is available from outcome clinical trials that would justify initiating drug therapy in patients with diabetes and high normal BP. Recent analyses indicate that optimal reduction of the global CV risk in most patients with hypertension and diabetes is obtained by lowering BP below 140/85 mm Hg. The change of the target DBP value has been based on an analysis of HOT and UKPDS study findings. Benefits of BP lowering below 130/80 mm Hg in diabetic patients have not been confirmed in the ACCORD and INVEST studies and are debatable also in patients with concomitant diabetic nephropathy.

Effective BP control in diabetic patients is difficult and thus these patients more often require combined antihypertensive drug therapy. Due to a proven nephroprotective effect of RAAS inhibitors, ACEI or ARB should be an invariable component of combination therapy and the preferred choice in monotherapy. When choosing between ACEI and ARB in diabetic patients, results of the most recent metaanalysis of studies performed in this group of patients may be taken into consideration, showing a greater long-term cardioprotective effect of ACEI. For combined therapy, first choices should include an ACEI with a calcium antagonist (ACCOMPLISH) or a thiazide-like diuretic (ADVANCE). Recently reported results of the ADVANCE ON study showed for the first time that antihypertensive therapy with a fixed-dose combination (perindopril + indapamide) may yield long-term (10 years) outcome benefits.

Concomitant administration of two RAAS inhibitors (also including the renin inhibitor) should be avoided due to a higher risk of hyperkalaemia and worsening of renal function (ONTARGET and ALTITUDE studies).

The management of patients with hypertension and diabetes should be particularly targeted at improvement of all CV risk factors. This means a strong indication for a statin, and the need to consider possible benefits of acetylsalicylic acid (ASA) (Table 18).

Table 18. Antihypertensive treatment strategies in patients with diabetes

Antihypertensive drug therapy is recommended in patients with grade 1–3 hypertension
Target BP in patients with diabetes is < 140/85 mm Hg
The presence of proteinuria does not modify target BP
In diabetes, RAAS inhibitors (ACEI and ARB) are recommended due to a greater nephroprotective effect
Combined drug treatment is more often required to obtain good BP control
Thiazide diuretics (thiazide-like agents are preferred) and dihydropyridine calcium antagonists are recommended in combination with a RAAS inhibitor
It is not recommended to combine two RAAS inhibitors
Statin therapy is recommended
Acetylsalicylic acid may be considered

ACEI — angiotensin-converting enzyme inhibitors; ARB — angiotensin receptor blockers; BP — blood pressure; RAAS — renin–angiotensin–aldosterone system

5.6. Hypertension in patients with chronic kidney disease

Observational studies show a direct correlation between BP values and development of CKD. Protection from further progression of renal disease requires strict BP control (< 140/90 mm Hg) and reducing proteinuria as much as possible. Lowering BP below 130/80 mm Hg to delay albuminuria is questionable (ROADMAP study), and in patients with hypertension and concomitant nephropathy with large proteinuria it remains a domain of nephrologists.

Compared to other classes of antihypertensive medications, ACEI and ARB are more effective at reducing proteinuria and delaying progression of renal disease, and thus are indicated in patients with moderately reduced glomerular filtration rate (GFR) and/or proteinuria. Therapy should be started with low doses that are later cautiously increased to moderate ones, with monitoring of creatinine and potassium levels. Reduction of baseline estimated GFR (eGFR) by 30% during the first 4–12 weeks of therapy should be considered acceptable. ACEI and ARB should not be used in patients with acute kidney injury, and initiation of these drugs is not recommended, unless supervised by a nephrologist, in patients with CKD and eGFR below 30 ml/min/1.73 m^2.

Combined therapy using several antihypertensive drugs is usually required to reach target BP. Based on the results of the ACCOMPLISH study, it was shown that a combination of an ACEI with a calcium antagonist rather than a thiazide diuretic is more effective at preventing doubling of serum creatinine level and development of end-stage renal disease. The type and dose of a diuretic should be adjusted to renal function. Thiazide and thiazide-like diuretics should not be used in patients with eGFR below 30 mL/min, and loop diuretics should be used instead. Doses of loop diuretics should be increased with worsening of renal function.

In advanced CKD, mineralocorticoid receptor antagonists are not recommended, particularly in combination with ACEI/ARB, due to a risk of renal function worsening and development of hyperkalaemia. If mineralocorticoid receptor antagonists are used in this patient group, strict monitoring of potassium level is required. Combining two RAAS inhibitors is also not recommended despite potentially higher effectiveness in reducing proteinuria. The latter two therapeutic options should remain a domain of nephrologists.

5.7. Hypertension complicated by ischaemic heart disease

Hypertension is an important factor in the pathogenesis of IHD (accelerated atherosclerosis, left ventricular hypertrophy).

In patients with hypertension in whom BP is lowered below 140/90 mm Hg, a clear reduction of the CV event rate is seen compared to patients with on-treatment BP values above 140/90 mm Hg, regardless of the drug classes used.

Long-term data from the INVEST study showed that in both patients with strict BP control (SBP < 130 mm Hg) and those with uncontrolled BP (SBP > 140 mm Hg), outcomes were worse than in patients with SBP 130–140 mm Hg, confirming the existence of the J curve in this patient group.

Although optimal BP reduction is the most important factor, recommended antihypertensive drugs in patients with concomitant IHD are ACEI (preferred drugs of this class are perindopril — EUROPA study, ramipril — HOPE study, and zofenopril — SMILE 4 study) and beta-blockers, particularly in patients after a MI. If angina is present, calcium antagonists are also used. In patients with concomitant IHD, ARB are second-choice drugs (preferred ones are telmisartan — ONTARGET study, and in patients after a MI also valsartan — VALIANT study) in case of ACEI intolerance, based on the results of multiple metaanalyses comparing these two drug classes in regard to reduction of the risk of death and cardiac events.

5.8. Hypertension complicated by heart failure

Along with IHD, hypertension is one of the two major causes of HF. It often leads to left ventricular diastolic dysfunction and HF with preserved ejection fraction. It is also the most important modifiable risk factor for the development of HF, and thus preventing HF involves use of antihypertensive drugs. Diuretics, beta-blockers, ACEI, and ARB were shown to be beneficial in the prevention of HF, while calcium antagonists are less effective in this regard.

In advanced HF, hypertension becomes less problematic due to reduction of cardiac output in this condition, and higher BP values are prognostically favourable. Any antihypertensive therapy should be undertaken with consideration of the current guidelines on the management of HF, which means that the preferred drugs in this patient group are beta-blockers (only carvedilol, bisoprolol, metoprolol XR/CR, and nebivolol), ACEI (drugs studied in postinfarction left ventricular dysfunction include lisinopril, ramipril, trandolapril, and zofenopril), and aldosterone antagonists (eplerenone is the preferred drug). ARB are second-choice drugs in case of ACEI intolerance (preferred drugs of this class are candesartan and valsartan).

Diuretics are recommended in patients with clinical evidence of left- or right-sided HF. The preferred drugs are thiazide-like diuretics with greater natriuretic effect (chlorthalidone) and loop diuretics, which induce an even stronger natriuretic effect. Among the latter, torasemide is characterised by greater bioavailability, better absorption, and longer half-life compared to furosemide, and exerts an additional anti-aldosterone effect, which translated to increased clinical benefits observed in the non-randomised TORIC study (Table 19).

Table 19. Antihypertensive treatment strategies in patients with heart disease

Target BP in patients with heart disease is < 140/90 mm Hg, and the likelihood of a clinical J-curve effect is particularly high in this patient group
Preferred antihypertensive drugs in patients with ischaemic heart disease, and particularly after a myocardial infarction, are ACEI and beta-blockers, and in patients with angina also calcium antagonists
Preferred antihypertensive drugs in patients with heart failure are ACEI and beta-blockers, followed by aldosterone antagonists, and diuretics in symptomatic patients
In patients with ischaemic heart disease and/or heart failure, ARB are alternative second choice drugs in case of ACEI intolerance
In patients with AF with rapid ventricular response, beta-blockers and possibly non-dihydropyridine calcium antagonists are recommended as antihypertensive drugs
Every hypertensive patient with heart disease requires statin and acetylsalicylic acid
Every hypertensive patient with AF requires antithrombotic treatment, preferentially with a novel oral anticoagulant
In patients with a risk of de novo or recurrent AF, ACEI or ARB may be considered for antihypertensive drug therapy, and eplerenone may be considered in patients with concomitant heart failure

ACEI — angiotensin-converting enzyme inhibitors; AF — atrial fibrillation; ARB — angiotensin receptor blockers; BP — blood pressure

5.9. Hypertension complicated by atrial fibrillation

Hypertension is the most common condition coexisting with atrial fibrillation (AF), and it is considered a reversible cause of this arrhythmia. In patients with AF with rapid ventricular rate, beta-blockers and non-dihydropyridine calcium antagonists are recommended. In patients with hypertension who are at risk of de novo AF, ACEI or ARB should be considered, although studies that evaluated reduction of the risk of recurrent AF during treatment with these drugs yielded contradictory results. In hypertension complicated by IHD, the risk of AF recurrence is probably reduced by any effective antihypertensive drug, and if HF is present, the risk is reduced by eplerenone.

Each patient with hypertension and permanent or recurrent AF requires anticoagulation, preferably using oral anticoagulants other than vitamin K antagonists (dabigatran, rivaroxaban, apixaban), to prevent stroke. In patients using anticoagulants, good BP control is particularly important to reduce the rate of bleeding events associated with anticoagulant therapy.

5.10. Hypertension and prevention of stroke

Regardless of the type of therapy, effective BP lowering reduces stroke risk more effectively than the risk of IHD. Metaanalyses indicate, however, that beta-blockers are less effective and calcium antagonists are more effective at reducing stroke risk compared to other antihypertensive drug classes.

Long-term after stroke or a transient ischaemic attack, the goal of therapy should be normalisation of BP (target BP < 140/90 mm Hg should be reached slowly, and provided that treatment is well tolerated). The reported data indicate efficacy of thiazide-like diuretics (indapamide in the PATS study and combined with perindopril in the PROGRESS study) and ARB (eprosartan in the MOSES study) in the secondary prevention of stroke. In contrast, the effect of antihypertensive drug therapy on the severity of vascular dementia has not been documented. During each visit, BP should be measured in the standing position to avoid excessive BP falls.

Due attention should also be paid to other basic elements of secondary stroke prevention, such as lifestyle modification and treating risk factors, anticoagulation, use of antiplatelet agents, and surgical treatment of carotid artery stenosis.

In the acute phase of stroke, hypertension should only be treated if SBP exceeds 220 mm Hg or DBP exceeds 120 mm Hg, and the drug if choice in these circumstances is labetalol (or, if it is unavailable, intravenous agents with medium duration of action). BP should be slowly reduced to values not lower than 180/110 mm Hg.

In the SCAST study, no significant effect of antihypertensive drug therapy in the acute phase of stroke was found on CV events, including recurrent stroke.

Fibrinolytic therapy may be used if BP is lower than 185/110 mm Hg. On the second day after stroke, antihypertensive therapy may be initiated if BP is higher than 180 and/or 120 mm Hg (Table 20).

Table 20. Antihypertensive treatment strategies in stroke patients

Target BP in patients after a stroke or TIA is < 140/90 mm Hg. BP should be reduced slowly, with target values reached about 2 weeks after the acute event, provided that the treatment is well tolerated
Antihypertensive drug therapy for the secondary prevention of stroke should be based on a thiazide-like diuretic with a possible addition of an ACEI, or based on an ARB
In the elderly patients after a stroke or TIA, somewhat higher target BP may be considered
Other major components of secondary prevention are indicated, such as lifestyle changes and treatment of risk factors, anticoagulant and antiplatelet treatment, and surgical treatment of carotid artery disease (if indicated)
In the acute phase of stroke, treatment of hypertension is indicated only for BP > 220/120 mm Hg

ACEI — angiotensin-converting enzyme inhibitor; ARB — angiotensin receptor blockers; BP — blood pressure; TIA — transient ischaemic attack

5.11. Other concomitant conditions

5.11.1. Hypertension with sexual dysfunction

Erectile dysfunction is more common in hypertensives than in individuals with normal BP values. Sexual dysfunction is considered an independent CV risk factor and a possible marker of atherosclerosis.

Multiple studies showed that antihypertensive drug therapy using older generation diuretics and beta-blockers increases the risk of erectile dysfunction in men. Compared to these drugs, newer antihypertensive drug classes, i.e. ARB and ACEI, have a neutral or even beneficial effect on erectile function. In contrast to conventional beta-blockers, nebivolol exerts a vasodilatatory effect related to nitric oxide release. Several studies showed that nebivolol may have a more beneficial effect on erectile dysfunction in men compared to other beta-blockers.

5.11.2. Hypertension and chronic lung disease

No studies compared the effect of antihypertensive therapy using different drug classes on long-term outcomes in patients with concomitant COPD.

However, knowledge of pharmacologic properties and adverse drug effect registries indicates that calcium antagonists and ARB may be considered safe antihypertensive drugs in patients with COPD. Caution is required when using ACEI (cough inducing bronchospasm) and beta-blockers (bronchospasm). If a drug from the latter class is required, its choice must be carefully dictated by cardioselectivity or additional protective properties, and attention must be paid to the recommended dose to minimise the effect on lung ventilation parameters. Cardioselective beta-blockers were found to reduce mortality among patients with COPD and concomitant cardiac disease.

5.11.3. Hypertension and glaucoma

The safest antihypertensive drugs that are not associated with a risk of glaucoma incidence and progression are beta-blockers.

Among the risk factors for glaucoma, in addition to high BP, an increasing attention has been paid to systemic hypotension which may lead to reduced perfusion of the optic disc and induce glaucoma lesions. It seems that systemic hypotension is a much more important risk factor for progression of visual field defects than hypertension. Thus, overly aggressive antihypertensive therapy may lead to progression of glaucoma. Most importantly, adverse effects of antihypertensive therapy include excessive nocturnal BP fall with secondary reduction of ocular perfusion. In patients with glaucoma, evening dosing of antihypertensive drugs is contraindicated unless ABPM shows very high BP values during the night.

5.11.4. Hypertension and gout

The preferred choice for antihypertensive therapy in patients with concomitant gout is losartan, as this drug reduces hyperuricaemia, which might be of importance for the reduction of CV risk (LIFE study), but there are no contraindications for other ARB, ACEI, and calcium antagonists in patients with hyperuricaemia. In contrast, drugs that increase serum acid level,

mostly thiazide/thiazide-like diuretics and beta-blockers, are not recommended. Allopurinol, which is used for long-term therapy of gout, may also be considered in hypertensives with asymptomatic hyperuricaemia, particularly those with CVD, due to a proven beneficial effect of this drug on the improvement of endothelial function and aortic compliance.

5.11.5. Hypertension and benign prostatic hyperplasia

When treating hypertension in men with benign prostatic hyperplasia, the general principles of antihypertensive therapy in the elderly using major drug classes should apply, and the previous recommendation to initiate therapy with an alpha-blocker has been abandoned after the ALLHAT study. The decision to use an alpha$_1$-adrenergic receptor antagonist to improve micturition should be made by an urologist, with consideration of uroselective drugs (e.g., tamsulosin) for better cardiac safety in patients on established antihypertensive therapy. Non-selective alpha$_1$-blockers (e.g., doxazosin) are among useful third- and fourth-line antihypertensive drugs, particularly in resistant hypertension (ASCOT study).

5.11.6. Hypertension and psoriasis

The prevalence of hypertension in patients with psoriasis is increased compared to the general population, as is resistance to treatment. The pathogenesis of hypertension in patients with psoriasis is related, among other factors, to systemic inflammation. Beta-blockers should be avoided in hypertensives with psoriasis and no concomitant IHD, as these drugs may worsen psoriasis.

5.11.7. Hypertension in the perioperative period

Preoperatively, it is not desirable to aim for full BP normalisation by intensifying previous therapy. Target BP values may be in the range of 140–160/90–100 mm Hg (due to an additional BP-lowering effect of anaesthetics).

Previous antihypertensive drug therapy may be generally continued, with usual morning dose of BP-lowering drugs. If possible, withholding diuretics 2–3 days before a major surgery should be considered (due to potential adverse effects related to fluid loss and hypokalaemia), and maybe also RAAS inhibitors on the day of the surgery (with the last dose taken on the day before the surgery). In the recent years, controversies have arisen around the use of beta-blockers in the perioperative period. Potential benefits of these drugs are limited to patients with a history of MI or with HF, and thus patient populations in which long-term use of beta-blockers is indicated anyway. In other patients, initiating beta-blocker therapy, particularly several days before the surgery, may be associated with an increased mortality risk. In the recent ESC guidelines, more consideration has been given to perioperative statin than beta-blocker use.

5.12. Resistant hypertension

Resistant hypertension is defined as BP values ≥ 140/90 mm Hg during appropriate combination therapy with three drugs (including a diuretic) in adequate doses.

Using this definition, resistant hypertension is a common clinical problem. In Poland, the proportion of patients with resistant hypertension has been estimated at 10–13% of all treated hypertensives. Patients with resistant hypertension are characterised by an increased CV risk compared to those with good on-treatment BP control. Cardiovascular risk is also related to the number of antihypertensive drugs used.

Most commonly, pseudoresistance to treatment is observed due to the following reasons:

- non-compliance;
- inappropriate drug treatment — too low drug doses, drug combinations including no diuretic;
- BP increase in office measurements (white coat effect);
- errors during BP measurement;
- pseudohypertension.

The most common identifiable and correctable reasons for treatment resistance include:

- lack of appropriate lifestyle modifications, including body weight increase and consumption of large amounts of alcohol;
- taking medications and substances that raise BP (e.g., non-steroidal anti-inflammatory drugs, glucocorticosteroids, cocaine, licorice etc.);
- undiagnosed secondary hypertension; common causes include obstructive sleep apnoea, renal disease, primary hyperaldosteronism, and renal artery stenosis;
- volume overload due to inappropriate diuretic treatment, progressive renal dysfunction, and large sodium intake;
- advanced, irreversible vascular damage leading to a significant increase in the arteriolar wall-to-lumen ratio or reduced large artery compliance.

After excluding these often difficult-to-eliminate causes, the prevalence of true resistant hypertension is much lower. In patients with true resistant hypertension, SBP values are usually very high, and the prevalence of severe left ventricular hypertrophy and renal dysfunction is increased.

5.12.1. Drug therapy of resistant hypertension

The algorithm for the management of resistant hypertension is shown in Table 21 and Figure 7.

The recommended and effective three-drug combination includes a RAAS inhibitor, thiazide/thiazide-like diuretic, and a calcium antagonist. In some patients with resistant hypertension, changing previous medications to this three-drug combination, also using fixed-dose combined preparations, may be associated with an improvement of BP control. In resistant hypertension, a good response has been seen to a mineralocorticoid receptor antagonist as the

Table 21. Antihypertensive treatment strategies in patients with resistant hypertension

Pseudoresistance should be excluded and correctable causes of treatment resistance should be eliminated before institution of additional therapy
In patients who are unsuccessfully treated with a RAAS inhibitor, diuretic, and calcium antagonist in maximal doses, an aldosterone antagonist should be added
The next step should be addition of an alpha-blocker (doxazosin) or a beta-blocker (vasodilatatory agents are preferred)
The next step should be substitution of a loop diuretic for thiazide/thiazide-like diuretic, particularly in patients with severe kidney dysfunction
As the next step, addition of a direct arteriolar vasodilator (hydralazine) or a central acting agent (clonidine) should be considered
In exceptional cases of truly resistant hypertension, after all the above drug treatment measures have been tried, invasive treatment (renal denervation) may be considered
Patient selection for renal denervation should be a domain of hypertension specialists, and these procedures should be performed by invasive cardiologists in specialised centres

RAAS — renin–angiotensin–aldosterone system

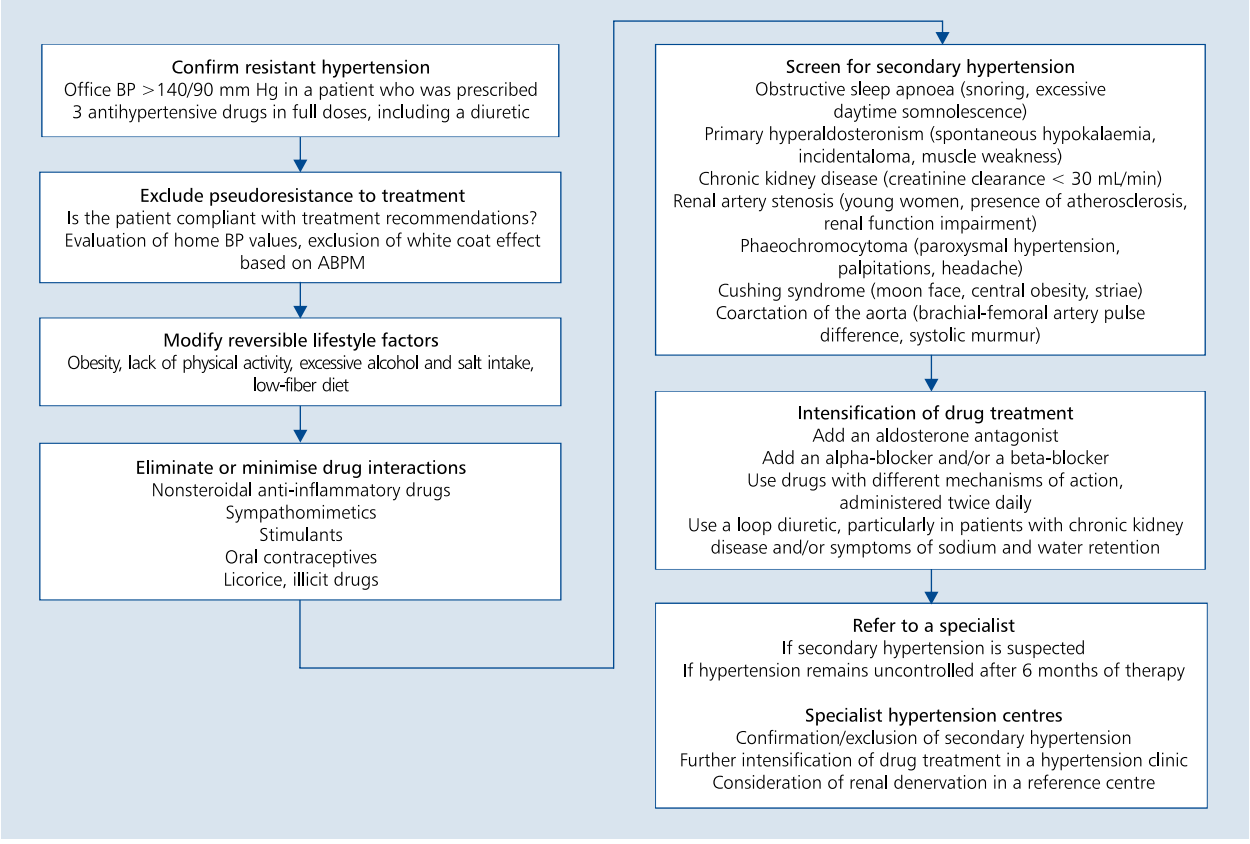

Figure 7. Management algorithm in resistant hypertension; ABPM — ambulatory blood pressure measurements; BP — blood pressure

next treatment step, particularly spironolactone, even in low doses (25–50 mg/day). An alpha-blocker (doxazosin) or beta-blocker may also be considered. In regard to the choice of a beta-blocker, benefits of vasodilating beta-blockers (carvedilol, nebivolol) have been highlighted. As the next step, it may be worth using a loop diuretic, particularly torasemide, instead of a thiazide/thiazide-like diuretic, in particular in patients with renal dysfunction, and obligatorily in patients with eGFR below 30 mL/min/1.73 m^2. Of note, some older generation antihypertensive drugs may be effective in the treatment of resistant hypertension, i.e. direct arterial vasodilators (hydralazine) and central sympatholytic drugs (clonidine, rilmenidine).

In resistant hypertension, twice daily dosing of antihypertensive drugs is frequently necessary.

5.12.2. Renal denervation

Renal denervation is based on a solid theoretical background to expect effectiveness of this approach in the treatment of hypertension. Initial results of the Symplicity-HTN1 and

HTN2 studies indicated that this procedure is highly effective. In addition, a beneficial effect on the glycaemic profile and improvement of the apnoea–hypopnea index in patients with obstructive sleep apnoea was seen. The interest in renal denervation and its importance as the last-resort therapy of resistant hypertension decreased significantly with the publication of the results of the randomised Symplicity-HTN3 study, showing no significant BP-lowering effect at 6 months of follow-up. Although further analyses showed higher efficacy of renal denervation in Caucasians, patients below 65 years of age, those without renal failure and treated with an aldosterone antagonist, even in these patient groups the overall BP reduction was modest, below 10 mm Hg. However, the procedure was shown to be safe. In contrast, the randomised PRAGUE-15 study showed that renal denervation is equally effective at lowering BP as adding spironolactone, and the randomised DENERHTN study showed that in patients with resistant hypertension despite use of a RAAS inhibitor, a calcium antagonist and a diuretic, denervation was associated with more effective BP lowering than adding further antihypertensive medications, including spironolactone.

According to the current expert opinion on renal denervation in the treatment of hypertension in Poland, published before the results of Symplicity-HTN3, PRAGUE-15 and DENERHTN studies were reported, this procedure is indicated for office SBP ≥ 160 mm Hg (mean of three measurements) during treatment with at least three antihypertensive medications in full doses, including a diuretic. Secondary

Clinical profile	Blood pressure [mm Hg]			
	High normal (130–139/85–89)	Grade 1 hypertension (140–159/90–99)	Grade 2 hypertension (160–179/100–109)	Grade 3 hypertension (≥ 180/110)
No risk factors				
1–2 risk factors		Statin LDL < 115 mg/dL	Statin LDL < 115 mg/dL	Statin LDL < 100 mg/dL
≥ 3 risk factors		Statin LDL < 115 mg/dL	Statin LDL < 100 mg/dL	Statin LDL < 100 mg/dL
Target organ damage, diabetes, CKD stage 3	Statin LDL < 100 mg/dL	Statin LDL < 100 mg/dL	Statin LDL < 100 mg/dL	Statin LDL < 100 mg/dL
Overt cardiovascular disease, CKD stage ≥ 4	Statin LDL < 70 mg/dL	Statin LDL < 70 mg/dL	Statin LDL < 70 mg/dL	Statin LDL < 70 mg/dL

Figure 8. Indications for statin therapy in hypertensive patients in relation to the global cardiovascular risk
CKD — chronic kidney disease (stage 3: eGFR 30–59 mL/min/1.73 m^2; stage ≥ 4: eGFR < 30 mL/min/1.73 m^2); LDL — low density lipoprotein

Clinical profile	Blood pressure [mm Hg]			
	High normal (130–139/85–89)	Grade 1 hypertension (140–159/90–99)	Grade 2 hypertension (160–179/100–109)	Grade 3 hypertension (≥ 180/110)
No risk factors				ASA (after BP is normalized!)
1–2 risk factors				ASA (after BP is normalised!)
≥ 3 risk factors			ASA (after BP is normalised!)	ASA (after BP is normalised!)
Target organ damage, diabetes, CKD stage 3	ASA	ASA (after BP is normalised!)	ASA (after BP is normalised!)	ASA (after BP is normalised!)
Overt cardiovascular disease, CKD stage ≥ 4	ASA	ASA	ASA	ASA

Figure 9. Indications for the treatment with acetylsalicylic acid (ASA) in hypertensive patients in relation to the global cardiovascular risk
BP — blood pressure; CKD — chronic kidney disease (stage 3: eGFR 30–59 mL/min/1.73 m^2; stage ≥ 4: eGFR < 30 mL/min/1.73 m^2)

hypertension, and in particular primary hyperaldosteronism, should be excluded in these patients. Following release of the Symplicity-HTN3 study, it seems reasonable to add spironolactone to drug treatment in patients who are considered candidates for renal denervation.

Currently, pending confirmation of the long-term effectiveness of renal denervation, it is recommended that patient selection for this procedure should be limited to specialised hypertension units, and these procedures should be performed by experienced invasive cardiologists.

6. TREATMENT OF CONCOMITANT RISK FACTORS (NON-BP-LOWERING THERAPY)

6.1. Lipid-lowering drugs

Hypercholesterolaemia is more prevalent in hypertensive patients compared to the general population, as is atherogenic dyslipidaemia in patients with concomitant diabetes. Multiple clinical trials on the use of statins in primary and secondary prevention, in which hypertensive patients constituted a significant proportion of the study populations, indicate that an optimal reduction of the global CV risk may be obtained by simultaneous reduction of BP and low density lipoprotein cholesterol (LDL-C) level. In patients with hypertension and CVD, statin treatment is mandatory based on the general guidelines of cardiac societies that recommend serum LDL-C level lowering below 70 mg/dL. Based on the results of recent randomised clinical trials, systematic reviews, and metaanalyses, optional LDL-C level lowering below 55 mg/dL has been even suggested in patients at the highest CV risk.

Initiation of statin treatment is also recommended in all high and very high risk patients (10-year risk of a CV event > 20%) without overt CVD regardless of the degree of BP elevation (atorvastatin in the ASCOT study), aiming for target serum LDL-C level below 100 mg/dL, and according to some societies below 70 mg/dL. In the ASCOT study, it was also shown that adding a statin to amlodipine- and perindopril-based antihypertensive treatment reduced the CV event rate more than adding a statin to atenolol- and thiazide diuretic-based treatment. Statin should also be used in hypertensive patients with moderate CV risk (> 15–20%; rosuvastatin in the JUPITER study), even in case of moderate hypercholesterolaemia, aiming for target serum LDL-C level below 115 mg/dL (Fig. 8).

6.2. Antiplatelet therapy

In patients with hypertension and CVD, use of ASA is mandatory based on the general guidelines of cardiac societies that recommend a 75 mg dose. In these cases, ASA treatment should be used regardless of the degree of BP control. A useful fixed-dose combination product in these patients is a combination of beta-blocker and ASA (bisoprolol + ASA).

A recently published large metaanalysis that evaluated the rates of major bleeding events in patients receiving long-term ASA treatment has changed the approach to the use of this drug in primary prevention. It has been shown that the net benefits of ASA, measured as the difference between the CV event rate reduction and the increase in the major bleeding event rate, have not been clearly established in this patient population. Thus, use of ASA for this indication requires evaluation of the risk-to-benefit ratio. Based on these recent reports, a low ASA dose should be considered only in hypertensive patients with a high (20–30%) or very high (> 30%) global CV risk. To minimise the risk of haemorrhagic stroke, it is recommended to initiate ASA treatment in these patients only after elevated BP has been fully controlled (Fig. 9). In view of these increasing limitations regarding the use of ASA in primary prevention, alternative substances with antiaggregant properties that have been evaluated in clinical trials (e.g., standardised tomato extract which exerts a weaker antiplatelet effect compared to ASA but has a more pleiotropic activity range) may be considered in patients with uncomplicated hypertension and moderate to high CV risk.

References *(153 items) available at: Nadciśnienie Tętnicze w Praktyce, 2015; 1, 1: 1–70.*